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Polychlorinated Biphenyls Ambient Water Quality Criteria

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POLYCHLORINATED BIPHENYLS

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for polychlorinated biphenyls. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi....

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CRITERION DOCUMENT

POLYCHLORINATED BIPHENYLS

Criteria

Aquatic Life

For polychlorinated biphenyls the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0015 µg/l as a 24-hour average and the concentration should not exceed 6.2 µg/l at any time.

For polychlorinated biphenyls the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.024 µg/l as a 24-hour average and the concentration should not exceed 0.20 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to PCBs through ingestion of water and contaminated aquatic organisms, the ambient water concentration should be zero. Concentrations of PCBs estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.26 ng/l, 0.026 ng/l and 0.0026 ng/l respectively.

Introduction

Polychlorinated biphenyls (PCBs) are the chlorinated derivatives of a class of aromatic organic compounds called biphenyls and are manufactured by the direct chlorination of the biphenyl ring system. The commercial products are complex mixtures of chlorobiphenyls and are marketed for various uses according to the percentage of chlorine in the mixture. Currently there is no production of PCBs in the United States but the sole producer of PCBs in the United States previously marketed four mixtures containing 21 percent, 41 percent, 42 percent and 54 percent chlorine for use only in closed electrical systems under the trademark "Aroclor." Prior to 1971 mixtures containing up to 68 percent chlorine were used in a number of other applications, including plasticizers, heat transfer fluids, hydraulic fluids, fluids in vacuum pumps and compressors, lubricants, and wax extenders.

In 1974 approximately 65 to 70 percent of domestic sales were to manufacturers of capacitors and the remainder to manufacturers of transformers while approximately 450,000 pounds of PCBs were imported primarily for use in non-closed systems. U.S. production appeared to be one-half of the world total.

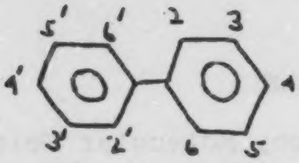
As a result of the long life of many products containing PCBs, it is believed that a substantial portion of the PCBs manufactured before 1971 are still in service and thus represent potential pollution through possible future discharge into the environment.

During the period 1972 to 1974 domestic production of PCBs averaged approximately 40 million pounds per year with 33 million pounds representing the annual domestic marketed consumption during that period.

Although the environmental behavior and biological activity of a number of individual chlorobiphenyl isomers have been studied in recent years, it is still difficult to evaluate the potential toxicity of the complex mixtures actually found in the environment since their composition often changes. In making this evaluation it is necessary to weigh carefully the results of studies of individual compounds, and to compare critically the environmental and toxicological properties of the commercial mixtures.

A further complication is that several commercial PCB mixtures have been reported to contain small quantities of highly toxic contaminants, polychlorinated dibenzofurans (PCDFs). Certain of the toxic effects observed in animals and humans exposed to PCBs appear to be attributable to PCDFs, while others appear to be caused by PCBs themselves. There is also some evidence that small quantities of PCDFs may be formed from PCBs while in service or as a result of metabolic changes in certain organisms.

PCBs consist of a mixture of chlorinated biphenyls which contain a varying number of substituted chlorine atoms on the aromatic rings. The biphenyl molecule has a total of ten sites where chlorine substitution can be accommodated as shown in the following structure:



The potential positions for chlorine substitution are numbered according to the American Chemical Society standard notation. Chlorinated biphenyls having the same number of chlorine atoms per molecule are referred to as a specific class of chlorobiphenyls, with a suitable numerical prefix to define the number of substituted chlorines. Hence, there are classes varying from monochlorobiphenyls to decachlorobiphenyl. All compounds within the same class have the same molecular weight and are structural isomers of each other. They differ only in terms of the location of the chlorine atoms in the biphenyls ring. The ten classes of chlorobiphenyls, comprissing 209 possible isomers, are summarized in Table 1.

Chlorobiphenyls with five or more chlorine atoms are referred to as "higher chlorobiphenyls." This distinction is made in recognition of the fact that the former group of compounds is much more persistent in the environment than the latter group. The tetrachlorobiphenyls are intermediate in persistence.

The physical properties of individual chlorinated biphenyls are known (Cook, 1972). The physical properties of the Aroclor mixtures are summarized in Table 2. Lower chlorinated Aroclors (1221, 1232, 1016, 1242, and 1248) are colorless mobile oils. Increasing chlorine content results in mixtures taking on the consistency of viscous liquids (Aroclor 1254) or sticky resins (Aroclors 1260 and 1262). Aroclors 1268 and 1270 are off white-white powders. With the exception of Aroclors 1221 and 1268, Aroclors do not crystallize upon

TABLE 1

Emperical Formulation, Molecular Weights and Chlorine Percentage in PCBs

Empirical formula chlorobiphenyls	Molecular weight*	Percent chlorine*	No. of isomers
$C_{12}H_{10}$	154	0	1
$C_{12}H_9Cl$	188	18.6	3
$C_{12}H_8Cl_2$	222	31.5	12
$C_{12}H_9Cl_3$	256	41.0	24
$C_{12}H_6Cl_4$	290	48.3	42
$C_{12}H_5Cl_5$	324	54.0	46
$C_{12}H_4Cl_6$	358	58.7	42
$C_{12}H_3Cl_7$	392	62.5	24
$C_{12}H_2Cl_8$	426	65.7	12
$C_{12}H_1Cl_9$	460	68.5	3
$C_{12}Cl_{10}$	490	79.9	1

*Based on Cl

TABLE 2

Physical Properties of Commercial PCBs (Aroclors)

Property	1221	1232	1016	1242	1248
Chlorine, percent	20.5-21.5	31.4-32.5	41	42	48
Specific Gravity	1.182-1.192 ($25^{o}/15.5^{o}C$)	1.270-1.280 ($25^{o}/15.5^{o}C$)	1.362-1.372 ($25^{o}/15.5^{o}C$)	1.391-1.392 ($25^{o}/15.5^{o}C$)	1.405-1.415 ($65^{o}/15.5^{o}C$)
Distillation Range C Corrected	275-320	290-325	323-356	325-366	340-375
Vapor Pressure (mm/HS)				$4.06x10^{-4}$	$4.94x10^{-4}$
Evaporation loss (%) 100 C 6 hr.	1.0-1.5	1.0-1.5		0-0.4	0-0.3
USTA D-6 Mod. 160 C, 5 hr.				3.0-3.6	3.0-4.0
Pour Point C (WTM E97) F	1 (Crystal) 34 (Crystal)	-35.5 -32		-19 2	-7 19.4
Water Solubility at 25 C(μg/l)	>200		225-250	240	54

Reference: Versar, Inc. (1976)
Hammond, et al. (1972)
Hutzinger, et al. (1974)
Mieuer, et al. (1976)
Tucker, et al. (1975)
Mackay and Wolkoff (1973)

TABLE 2 (cont)

Physical Properties of Commercial PCBs (Aroclors)

Property	1254	1260	1262	1268	1270
Chlorine, percent	54	60	61.5-62.5	68	71
Specific Gravity	1.495-1.555 (65°/15.5°C)	1.555-1.566 (90°/15.5°C)	1.572-1.583 (90°/15.5°C)	1.604-1.611 (25°/25°C)	1.944-1.960 (25°/25°C)
Distillation Range C Corrected	365-390	385-420	390-425	435-450	450-460
Vapor Pressure (mm/HS)	$7.71x10^{-5}$	$4.05x10^{-5}$			
Evaporation loss (%) 100 C 6 hr.	0-0.2	0-0.1	0-0.1	0-0.6	
USTA D-6 Mod. 160 C, 5 hr.	1.1-1.3	0.5-0.8	0.5-0.2	0.1-0.2	
Pour Point C (WTM E97) F	10 50	31 88	35-38 99		
Water Solubility at 25 C(ug/l)	12	2.7			

heating or cooling but at a specific temperature, definesd as a "pour point," change into a resinous state.

It is known from the studies of pesticides that soil moisture and evaporation of water have a strong influence on the rate of chlorinated hydrocarbon volatilization from soils and sand. Haque, et al (1974) demonstrated that the periodic evaporization of water from Ottawa sand enhanced the total volatilization of Aroclor 1254 but reduced the degree of differentiation in the volatility of the higher chlorinated biphenyls (7,6, and 5 chlorine aroms) from the tetrachlorobiphenyls. However, when Aroclor 1254 was heated in water at 100°C the total volatilization of this Aroclor was reduced compared to equivalent dry isothermal conditions but the differentiation in volatility between the higher and lower chlorinated biphenyls was increased (Bowes, et al. 1975a).

Mackay and Wolkoff (1973) calculated theoretical evaporation rates for various Aroclors from water and predicted very rapid volatilization rates. Under laboratory conditions, PCBs appear to volatilize fairly rapidly from water in aquaria (Uhlken, et al. 1973) and even from flasks plugged with glass wool (Oloffs, et al. 1972). Under the same conditions, volatilization was markedly reduced in the presence of sediments (Oloffs, et al. 1973). Hence in natural waters, it would seem likely that absorption to sediments would limit the rate of volatilization.

Solubilities of the individual chlorinated biphenyls in water have been studied by several workers and an inverse correlation between solubility and degree of chlorination has been reported (Wollnöfer, et al. 1973; Haque and Schmedding, 1975; Metcalf, et al. 1975). The problem in obtaining true solution equilibria data for PCBs in water has been explained by Schoor (1975) who has given evidence that solutions of PCBs in water are in fact stable emulsions of PCB aggregates and that the true solubility of Aroclor 1254 is less than 0.1 µg/l in fresh water and 0.04 µg/l in marine water.

Chlorobiphenyls are freely soluble in relatively nonpolar organic solvents (Hutzinger, et al. 1974) and lipids in biological systems (Hammond, et al. 1972; Metcalf, et al. 1975). Metcalf, et al. (1975) have reported parition coefficients between octanol and water in the range of 10,000 to 20,000 for representative tri-, tetra-, and pentachlorobiphenyls. Partition coefficients with this biphasic solvent system have been found to correlate well with ecological magnification factors in aquatic organisms (Metcalf, et al. 1975).

PCBs are strongly adsorbed on solid surfaces, including glass and metal surfaces in laboratory apparatus (Schoor, 1975) and soils, sediments, and particulates in the environment (Haque, et al. 1974; Oloffs, et al. 1973; Crump-Wiesner, et al. 1974; Dennis, 1976; Munson, et al. 1976; Pfister, et al. 1969).

In aquatic environments, PCBs are associated with sediments and are usually found at much higher concentrations in sediments than in water in contact with them (Young, et al. 1976;

Crump-Weisner, et al. 1974; Dennis, 1976). As with other chlorinated hydrocarbons, PCBs are probably associated particularly strongly with micro-particulates of 0.15 µm diameter or less (Pfister, et al. 1969).

PCBs are commercially produced by the chlorination of the biphenyl ring with anhydrous chlorine in the presence of iron filings or ferric chloride as the catalyst. The crude product is purified to remove color, traces of the byproduct hydrogen chloride, and the catalyst by treatment with alkali and subsequent distillation. The purified product is a complex mixture of the chlorobiphenyls, the precise composition depending on the conditions under which the chlorination occurred.

It has been reported that foreign PCB mixtures are similar in composition to one of the 10 Aroclor products previously manufactured in the U.S. Gas liquid chromatograms of Phenoclor DP6 (France), Clopen A60 (Germany), and Aroclor 1260 (U.S.), all mixtures containing 60 percent chlorine, show that these mixtures are virtually identical (Taş and de Vos, 1971). Jensen and Sundstron (1974) have shown that Clophen A60 and A50 (Germany) are very similar in isomer composition to Aroclors 1260 and 1254 (U.S.) respectively. Table 3 lists the distribution of the various classes of chlorobiphenyls in seven major Aroclor mixtures as reported by Mieure, et al. (1976) Webb and McCall (1973), and Hirwe, et al. (1974). The small differences in analytical results reported for Aroclors 1242 and 1254 may reflect either differences in analytical methods or variations in sample constitution.

TABLE 3

Approximate Molecular Composition of Aroclors

Chlorobiphenyl	1221		1232		1242			1248		1254		1260
	M	W	W	M	M	W	H	W	M	W	H	W
$C_{12}H$	11	7	6	Tr	Tr	-	-	-	Tr	-	-	-
$C_{12}H_{10}Cl$	51	51	26	1	1	1	Tr	-	Tr	-	-	-
$C_{12}H_9Cl_2$	32	38	29	20	16	17	4	1	0.5	-	-	-
$C_{12}H_8Cl_3$	4	3	24	57	49	40	39	23	1	-	0.5	-
$C_{12}H_7Cl_4$	2	-	15	21	25	32	42	50	21	16	36	-
$C_{12}H_6Cl_5$	0.5	-	0.5	1	8	10	14	20	48	60	45	12
$C_{12}H_5Cl_6$	-	-	-	Tr	1	0.5	-	1	23	23	18	46
$C_{12}H_4Cl_7$	-	-	-	-	Tr	-	-	-	6	1	1	36
$C_{12}H_3Cl_8$	-	-	-	-	-	-	-	-	-	-	-	6
$C_{12}H_2Cl_9$	-	-	-	-	-	-	-	-	-	-	-	-
$C_{12}H\ Cl_{10}$	-	-	-	-	-	-	-	-	-	-	-	-

Tr - Trace (less than 0.1 percent) Letters refer to references

Reference: Micure, et al. (1976)
Webb and McCall (1973)
Hirwe, et al. (1974)

Certain substitution patterns are believed to influence the biological activities of chlorobiphenyls. The presence of two adjacent carbon atoms without chlorine substitution in one or both rings is believed to facilitate metabolism because it permits the formation of arene oxide intermediates (Safe, et al. 1975). Essentially all chlorobiphenyls with five or fewer chlorine atoms have at least one pair of adjacent unsubstituted carbon atoms because of the rarity of 3,5-substitution in the natural mixtures.

Jensen and Sundstrom (1974b) presented evidence that chlorobiphenyls with three or four chlorine atoms in the ortho-positions (2- and 6- positions) are more easily metabolized by humans than those with only one or two ortho-chlorines. Compounds with three or four ortho-substituted chlorines are virtually absent from Aroclors 1016 and 1242 but are fairly well represented in Aroclors 1254 and 1260 (Clopens A50 and A60 respectively).

McKinney (1976) has suggested that chlorobiphenyl isomers with chlorine substitution in both the 4- and 4' positions tend to be biologically active and well retained in tissues. The number and proportion of these isomers increase with increasing mixture chlorination.

McKinney, et al. (1976a) have shown an association between biological activity and substitutions in the 3,4-, or 3,4,5- positions on one or both rings. The first pattern is frequently found in PCB mixtures but the second is found only as part of the 2,3,4,5-pattern which is found in only trace amounts in PCBs.

Toxic materials other than chlorinated biphenyls have been found in commercial PCB mixtures. Vos, et al. (1970), Bowes, et al. (1975a), Roach and Pomerantz (1974), Nagayama, et al. (1976), and Kuratsume, et al. (1976) have detected polychlorinated dibenzofurans (PCDFs) in a number of domestic and foreign PCB mixtures at levels of 0.8 to 33 mg/kg. While 119 structurally different PCDF isomers are possible, only two have been precisely identified to date, the 2,3,7,8-tetrachloro- and the 2,3,4,7,8-pentachlorodibenzofurans (Bowes, et al. 1975).

Polychlorinated naphthalenes (PCNs) have also been identified in small quantities in Clopen A60 and Phenochlor DP 6 (both corresponding to Aroclor 1260), Aroclor 1254, and KC-400 (corresponding to Aroclor 1248) (Vos, et al. 1970; Roach and Pomerantz, 1974; Bowes, et al. 1975).

There appear to be no authenticated reports of polychlorinated dibenzo-p-dioxins (PCDDs) in commercial PCBs (Bowes, et al. 1975a). The presence of potentially toxic compounds other than polychlorinated biphenyls in commercial PCB mixtures complicates both analytical and toxicological evaluation of such mixtures.

PCBs are considered to be inert to almost all of the typical chemical reactions. PCBs do not undergo oxidation, reduction, addition, elimination, or electrophilic substitution reactions except under extreme conditions. Chlorines can be replaced by reductive dechlorination with any metal hydride such as lithium aluminum hydride but temperatures of 245°C or greater are required to effect chlorine displacement.

The reactions of environmental importance that PCBs appear to undergo include alkali- and photochemically-catalized nuceleophilic substitutions and photochemical free radical substitutions, all of which occur with alkali and water.

Photolysis generally has been found to give one type of product under environmental conditions (Hutzinger, et al. 1974; Ruzo, et al. 1972; Ruzo, et al. 1974a; Ruzo and Zabik, 1975; Hutzinger, et al. 1972c; Herring, et al. 1972). Chlorine is replaced by hydroxy groups in aqueous systems.

A marked increase in rate of PCB photolysis was observed when solvents were degassed prior to irradiation (Ruzo, et al. 1974a). Oxygen is known to act as a free radical quencher by accepting energy from free radicals before any chemical change can occur. This increase in rate therefore implies that a free radical process is occurring and in the environment these photochemical transformations will be enhanced under anaerobic conditions.

The photochemical behavior of higher chlorobiphenyls appears similar to that of the tetrachlorobiphenyls (Hutzinger, et al. 1972c; Herring, et al. 1972). Irradiation of Aroclor 1254 in aqueous solution gave rise to dechlorinated and hydroxylated products (Hutzinger, et al. 1972c). Hexa- and octachlorobiphenyls are more photochemically reactive than tetrachlorobiphenyls (Hutzinger, et al. 1972c), so that under irradiation the higher components of Aroclor 1254 are selectively degraded (Hutzinger, et al. 1972c; Herring, et al. 1972).

The creation of free radicals by sunlight allows the environmental replacement of chlorines by hydroxy groups from water without the intervention of alkali. When this occurs at the ortho position (found to the the most preferred for chlorine loss) the resulting 2-hydroxychlorobiphenyl is perfectly positioned to allow oxygen to bond to an ortho position of the other ring. This results in the creation of potentially the most important class of contaminant in commercial mixtures of PCBs, the chlorodibenzofurans (CDFs).

Irradiation studies on either Aroclor 1254 or 2,5,2', 5'-tetrachlorobiphenyl (Hutzinger, et al. 1972c) in hydroxylic solvents have shown the formation of phenolic compounds, carboxylic compounds, and polymers along with dechlorination. Activation of the phenyl rings by metals or metallic salts make them more susceptible to hydroxylation. Thus in the environment, either heat, light, or metals and metal salts in water could theoretically accelerate the transformation of PCBs to PCDFs. The ultraviolet component of sunlight is sufficiently energetic to generate free radicals from both phenols and PCBs. The energies required to break the Ar-Cl bond to form hydroxy-PCBs in a hydroxylic solvent and ArO-H bond to form CDFs correspond to wavelengths near 360 to 320 nm, respectively. These wavelengths are clearly within the sunlight region.

Irradiation experiments with five pure 2-chlorinated biphenyls as 5 mg/l aqueous suspensions, showed that traces of 2-chlorodibenzofuran were detectable although only the 2,5-dichloro- and the 2,5,2',5'-tetrachlorobiphenyls provided identifiable amounts or approximately a 0.2 percent yield during a seven-day irradiation (Crosby, et al. 1973; Crosby and Moilanen, 1973). The environmental significance of this is four fold: (1) ortho-chlorobiphenyls can be hydroxylated by radiation similar to sunlight when they are suspended in aqueous media; (2) the product(s) are converted to CDFs; (3) rates of CDF formation by this process are approximately the same as their rates of degradation, leading to an approximately steady concentration. The fourth point of significance is illustrated by irradiation studies on 2,8-dichlorobenzofuran (Crosby and Moilanen, 1973). Decomposition of this material was found to be very slow in aqueous suspension but dehalogenation did not take place to form the relatively photolytically stable 2-chlorodibenzofuran.

In addition to photochemical and metallic/metallic salt formations of PCDFs from PCBs, a third route of formation has been suggested. Kanechlor KC-400 (analogous to Aroclor 1248) having an intitial PCDF content of 20 mg/kg, was shown to undergo conversion as the heat transfer fluid in a heat exchanger to give PCBs with a PCDF content of 4975-11765 mg/kg (Nagayma, et al. 1976; Kuratsune, et al. 1976). This material was identified as the agent which poisoned a large number of Japanese in 1968. A general disadvantage of PCBs in many of their applications including electrical capacitor and transformer uses as well as heat transfer uses is their tendency to decompose under the action of heat or electrical arcing to form potentially more toxic products (Broadhurst, 1972).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Most data for polychlorinated biphenyls (PCB's) are for studies concerned with tissue levels in fish, mammals, and birds, without correlation with source or exposure concentrations. Many studies dealing with various physiological parameters are also available, but again, are such that they are of little use here. Also, PCB's often do not appear to be very acutely toxic to juvenile and adult freshwater fish and invertebrate species due to solubility problems in static tests, and this can lead to erroneous judgments as to the actual toxicity of the compounds.

PCB's occur as mixtures of chemical isomers that differ in the amount of chlorination of the biphenyl structure, they have been treated herein as a single entity. They are highly lipophilic and bioconcentrate to high tissue concentrations from water concentrations that are below the usual detection limits.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Acute Toxicity

Only three 96-hour LC50 values are available and these are for the fathead minnow (Table 1). Newly-hatched fish were more sensitive than juveniles with LC50 values of 15 µg/l and 300 µg/l, respectively, for Aroclor 1242 (A-1242). A-1254 was more toxic with an LC50 of 7.7 µg/l for newly-hatched fish. No adjustments to the data were necessary as all values were from flow-through tests with measured concentrations. Other 96-hour LC50 values in the literature exceeded the solubility of PCB's and were not used. The solubility of PCB's is, at most, 250 µg/l and 96-hour LC50 values such as 50,000 µg/l are meaningless.

The acute toxicity data base for invertebrate species (Table 2) contains 12 values for three species. These values were from static and flow-through tests and showed an LC50 range from 10 µg/l for the scud, Gammarus fasciatus, to 200 to 400 µg/l for the damselfly, Ischnura verticalis. The higher chlorinated isomers, such as Aroclor 1254 which contains 54 percent chlorine, were more toxic to Gammarus pseudolimnaeus, than they were to fish, with LC50 values of 73 µg/l for A-1242 and 29 µg/l for A-1248.

Acute toxicity tests with polychlorinated biphenyls have established that these compounds can be toxic to aquatic life at low concentrations once they are in solution. The data indicate that the more highly chlorinated compounds are more toxic to fish and invertebrate species. The Final Fish Acute Value is 7.7 µg/l and the Final Invertebrate Acute Value is 6.2 µg/l which also becomes the Final Acute Value.

Chronic Toxicity

Four flow-through chronic tests have been conducted with polychlorinated biphenyls and fathead minnows. Test concentrations were measured. The fish were most sensitive to A-1248 with a chronic value of 0.2 µg/l (Table 3). Chronic values for A-1242, A-1254, and A-1260, were 9.0, 2.9, and 2.3 µg/l, respectively. The geometric mean (1.86 µg/l) of the four chronic concentrations divided by the species sensitivity factor (6.7) results in a value of 0.28 µg/l. Since the lowest chronic value is 0.20 µg/l, it becomes the Final Fish Chronic Value.

Results from 14 chronic tests with 2 invertebrate species, _Daphnia magna_ and _Gammarus pseudolimnaeus_, are shown in Table 4. The low chronic values for _Daphnia magna_, 1.14 µg/l for A-1242, 1.4 µg/l for A-1248, and 0.73 µg/l for A-1254 were from flow-through tests with measured concentrations; the other values were from static tests, and were much higher due to loss of PCB's from the test containers. The two chronic values for _Gammarus pseudolimnaeus_, 4.9 µg/l for A-1242 and 3.3 µg/l for A-1248, were from flow-through tests with measured concentrations. The geometric mean of the 14 tests was 8.1 µg/l which, after division by the species sensitivity factor (5.1) results in a concentration of 1.6 µg/l. Since there is a lower chronic value (0.73 µg/l for _Daphnia magna_), this latter value becomes the Final Invertebrate Chronic Value.

Plant Effects

Results from six tests with four different algal species are shown in Table 5. In general the data show that plants were less sensitive than the fish and invertebrate species, but reduction in the rate of carbon fixation in *Scenedesmus quadricauda* occurred at 0.1 µg/l A-1254 which is lower than the Final Fish and Invertebrate Chronic Value. Therefore, the Final Plant Value is 0.1 µg/l.

Residues

Table 6 contains results of 25 laboratory residue studies and 47 field studies of fish residues where information on water concentrations was also available. The studies include laboratory and field data for invertebrate and fish species and show a wide range of bioconcentration factors (BCF's). For invertebrate species the BCF ranged from 740 for stoneflies exposed for 21 days to 125,000 for mysids collected from Lake Superior. The BCF for fish ranged from 3,500 for field collected bass to 4,125,000 for field-collected siscowet, a race of lake trout. For laboratory exposures, the BCF ranged from 5,500 for white sucker exposed for 30 days to 540,000 for minnows exposed for 240 days.

The residue limit established by the Food and Drug Administration (FDA) for polychlorinated biphenyls in edible fish and shellfish is 5.0 mg/kg. Significant effects on reproduction of mink were observed when fed food containing 0.64 mg/kg; this figure was used to calculate the Residue Limited Toxicant

Concentration (RLTC). Since fish is one of the principal foods of mink, the mink-effect concentration of 0.64 mg/kg was divided by the geometric mean fish bioconcentration factor of 427,000 to give an RLTC of 0.0000015 mg/kg or 0.0015 µg/l.

The lowest of the Final Fish Chronic Value (0.2 µg/l), Final Invertebrate Chronic Value (0.73 µg/l), Final Plant Value (0.1 µg/l) and the RLTC (0.0015 µg/l) is used to determine the Final Chronic Value. For polychlorinated biphenyls the Final Chronic Value is 0.0015 µg/l.

Miscellaneous

Data presented in Table 7 do not conflict with the selection of 0.0015 µg/l as the Final Chronic Value.

Criterion Formulation

Freshwater Aquatic Life

Summary of Available Data

Final Fish Acute Value + 7.7 μg/l

Final Invertebrate Acute Value = 6.2 μg/l

Final Acute Value = 6.2 μg/l

Final Fish Chronic Value = 0.20 μg/l

Final Invertebrate Chronic Value = 0.73 μg/l

Final Plant Value = 0.10 μg/l

Residue Limited Toxicant Concentration = 0.0015 μg/l

Final Chronic Value = 0.0015 μg/l

0.44 x Final Acute Value = 2.7 μg/l

The maximum concentration of polychlorinated biphenyls is the Final Acute Value of 6.2 μg/l and the 24-hour average concentration is the Final Chronic Value of 0.0015 μg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For polychlorinated biphenyls the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0015 μg/l as a 24-hour average and the concentrations should not exceed 6.2 μg/l at any time.

Table 1. Freshwater fish acute values for polychlorinated biphenyls (Nebeker, et al. 1974)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Fathead minnow (juvenile), *Pimephales promelas*	FT	M	A-1242	96	300	300
Fathead minnow (newly hatched), *Pimephales promelas*	FT	M	A-1242	96	15	15
Fathead minnow (newly hatched), *Pimephales promelas*	FT	M	A-1254	96	7.7	7.7

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* FT = flow-through

** M = measured

Geometric mean of adjusted values = 33 µg/l $\frac{33}{3.9}$ = 8.4 µg/l

Lowest value from a flow-through test with measured concentrations = 7.7 µg/l

Table 2. Freshwater invertebrate acute values for polychlorinated biphenyls

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Scud, *Gammarus fasciatus*	FT	M	A-1242	96	10	10	Mayer, et al. 1977
Scud, *Gammarus fasciatus*	S	U	A-1248	96	52	44	Mayer, et al. 1977
Scud, *Gammarus fasciatus*	S	U	A-1254	96	2,400	2,032	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	FT	M	A-1242	96	73	73	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	FT	M	A-1248	96	29	29	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	S	U	2,3,4-trichlorobiphenyl	96	70	59	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S	U	4,4-dichlorobiphenyl	96	100	85	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S	U	2,4-dichlorobiphenyl	96	120	101	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S	U	2,4,6,2',4',6-hexachlorobiphenyl	96	150	127	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S	U	2,4,5,2',5-pentachlorobiphenyl	96	210	178	Mayer, et al. 1977
Damselfly, *Ischnura verticalis*	FT	M	A-1242	96	400	400	Mayer, et al. 1977
Damselfly, *Ischnura verticalis*	FT	M	A-1254	96	200	200	Mayer, et al. 1977

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* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 131 µg/l $\frac{131}{21}$ = 6.2 µg/l

Lowest value from a flow-through test with measured concentrations = 10 µg/l

Table 3. Freshwater fish chronic values for polychlorinated biphenyls

Organism	Test *	Limits (µg/l)	Chronic Value (µg/l)	Reference
Fathead minnow, Pimephales promelas	LC	0.1 - 0.4 A-1248	0.2	DeFoe, et al. In press
Fathead minnow, Pimephales promelas	LC	1.3 - 4.0 A-1260	2.3	DeFoe, et al. In press
Fathead minnow, Pimephales promelas	LC	5.4 - 15 A-1242	9.0	Nebeker, et al. 1974
Fathead minnow, Pimephales promelas	LC	1.8 - 4.6 A-1254	2.9	Nebeker, et al. 1974

* LC = Life cycle or partial life cycle

Geometric mean of chronic values = 1.86 µg/l $\frac{1.86}{6.7}$ = 0.28 µg/l

Lowest chronic value = 0.2 µg/l

Application Factor Values (Nebeker, et al. 1974)

Species	96-hr LC50 (µg/l)	MATC (µg/l)	AF
Fathead minnow, Pimephales promelas	15.0 (A-1242)	9.0 (A-1242)	0.6
Fathead minnow, Pimephales promelas	7.7 (A-1254)	2.9 (A-1254)	0.38

Geometric mean AF = 0.48

Geometric mean LC50 = 10.75 µg/l

0.48 $\sqrt{7.7\ \mu g/l \times 10.75\ \mu g/l}$ = 4.4 µg/l

Table 4. Freshwater invertebrate chronic values for polychlorinated biphenyls

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Reference
Cladoceran, *Daphnia magna*	LC	10-24	15 A-1254	Maki & Johnson, 1975
Cladoceran, *Daphnia magna*	LC	89-125	105 A-1221	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	53-66	59 A-1232	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	48-63	55 A-1242	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	16-24	19 A-1248	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	18-28	22 A-1254	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	22-33	27 A-1260	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	24-41	31 A-1262	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	162-206	182 A-1268	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	1.0-2.1	1.4 A-1248	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	0.48-1.1	0.73 A-1254	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	1.0-1.3	1.14 A-1242	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	LC	2.8-8.7	4.9 A-1242	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	LC	2.2-5.1	3.3 A-1248	Nebeker & Puglisi, 1974

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* LC = Life cycle or partial life cycle

Geometric mean of chronic values = 8.1 µg/l $\frac{8.1}{5.1}$ = 1.6 µg/l

Lowest chronic value = 0.73 µg/l

Table 5. Freshwater plant effects for polychlorinated biphenyls

Organism	Effect	Concentration (µg/l)	Reference
Alga, *Chlamydomonas reinhardtii*	Reduced growth	2,000 A-1242	Morgan, 1972
Alga, *Chlorella pyrenoidosa*	Depressed cell productivity	1,000 A-1268	Hawes, et al. 1976b
Alga, *Chlorella pyrenoidosa*	Reduced population growth	1,000 A-1254	Hawes, et al. 1976a
Alga, *Euglena gracilis*	48 hr ID50	4,400 A-1221	Ewald, et al. 1976
Alga, *Scenedesmus obtusiusculus*	Growth inhibition	300 A-1242	Larsson & Tillberg, 1975
Alga, *Scenedesmus quadricauda*	Reduction in rate of carbon fixation	0.1 A-1254	Luard, 1973

Lowest plant value = 0.1 µg/l

Table 6. Freshwater residues for polychlorinated biphenyls

Organism	Bioconcentration Factor	Time (days)	Reference
Snail, *Physa* sp.	59,600	33	Sanborn, 1974
Snails,	45,000	Field data	Nadeau & Davis, 1976
Cladoceran, *Daphnia magna*	3,800	4	Mayer, et al. 1977
Mysid, *Mysis relicta*	125,000	Field data	Veith, et al. 1977
Scud, *Gammarus pseudolimnaeus*	6,200	21	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	108,000	60	Nebeker & Puglisi, 1974
Amphipod, *Pontiporeia affinis*	1,709	Field data	Haile, et al. 1975
Glass shrimp, *Palaemonetes kadiakensis*	2,600	21	Mayer, et al. 1977
Crayfish, *Orconectes nais*	750	21	Mayer, et al. 1977
Stonefly, *Pteronarcys dorsata*	740	21	Mayer, et al. 1977
Mosquito, *Culex tarsalis*	3,500	7	Mayer, et al. 1977
Phantom midge, *Chaoborus punctipennis*	2,700	14	Mayer, et al. 1977
Dobsonfly, *Corydalus cornutus*	1,500	7	Mayer, et al. 1977
Gizzard shad, *Dorosoma cepedianum*	150,300	Field data	Hesse, 1973
Alewife, *Alosa pseudoharengus*	270,000	Field data	Hesse, 1973

Table 6. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Alewife, Alosa pseudoharengus	89,000	Field data	Veith, 1975
Alewife, Alosa pseudoharengus	42,700	Field data	Haile, et al. 1975
Chub, Coregonus johannae	850,000	Field data	Hesse, 1973
Menominee, Prosopium cylindraceum	120,000	Field data	Hesse, 1973
Lake whitefish, Coregonus clupeaformis	110,000	Field data	Hesse, 1973
Lake whitefish, Coregonus clupeaformis	875,000	Field data	Veith, et al. 1977
Bloater, Coregonus hoyi	1,162,500	Field data	Veith, et al. 1977
Bloater, Coregonus hoyi	81,000	Field data	Veith, et al. 1977
Lake herring, Coregonus artedii	250,000	Field data	Veith, et al. 1977
Rainbow trout, Salmo gairdneri	120,000	Field data	Veith, 1975
Rainbow trout, Salmo gairdneri	46,000	30	Bills & Marking, 1977
Rainbow trout, Salmo gairdneri	5,850	42	Branson, et al. 1975
Steelhead trout, Salmo gairdneri	600,000	Field data	Hesse, 1973
Brook trout, Salvelinus fontinalis	47,000	118	Mauck, et al. In press
Brook trout, Salvelinus fontinalis	60,000	500	Snarski & Puglisi, 1976

Table 6. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Brown trout, *Salmo trutta*	119,000	Field data	Veith, 1975
Lake trout, *Salvelinus namaycush*	1,110,000	Field data	Hesse, 1973
Lake trout, *Salvelinus namaycush*	212,000	Field data	Veith, 1975
Lake trout, *Salvelinus namaycush*	2,333,000	Field data	Parejko, et al. 1975 Veith, et al. 1977
Lake trout, *Salvelinus namaycush*	1,625,000	Field data	Veith, et al. 1977
Siscowet, *S. namaycush siscowet*	4,125,000	Field data	Veith, et al. 1977
Chinook salmon, *Oncorhynchus tschawytscha*	1,240,000	Field data	Hesse, 1973
Chinook salmon, *Oncorhynchus tschawytscha*	240,000	Field data	Veith, 1975
Coho salmon, *Oncorhynchus kisutch*	173,000	Field data	Veith, 1975
Rainbow smelt, *Osmerus mordax*	462,500	Field data	Veith, et al. 1977
Rainbow smelt, *Osmerus mordax*	32,000	Field data	Veith, 1975
Rainbow smelt, *Osmerus mordax*	48,000	Field data	Haile, et al. 1975
Pike, *Esox lucius*	15,000	Field data	Hesse, 1973
Carp, *Cyprinus carpio*	43,600	Field data	Hesse, 1973
Carp, *Cyprinus carpio*	390,000	Field data	Hesse, 1973

Table 6. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Carp, *Cyprinus carpio*	110,000	Field data	Veith, 1975
Fathead minnow, *Pimephales promelas*	240,000	240	DeFoe, et al. In press
Fathead minnow, *Pimephales promelas*	120,000	240	Defoe, et al. In press
Fathead minnow, *Pimephales promelas*	270,000	240	DeFoe, et al. In press
Fathead minow, *Pimephales promelas*	540,000	240	DeFoe, et al. In press
Fathead minnow, *Pimephales promelas*	274,000	255	Nebeker, et al. 1974
Fathead minnow, *Pimephales promelas*	107,000	255	Nebeker, et al. 1974
Fathead minnow, *Pimephales promelas*	235,000	240	Nebeker, et al. 1974
Fathead minnow, *Pimephales promelas*	238,000	240	Nebeker, et al. 1974
Common shiner, *Notropis cornutus*	>78,000	Field data	Nadeau & Davis, 1976
Longnose sucker, *Catostomus catostomus*	150,000	Field data	Hesse, 1973
Longnose sucker, *Catostomus catostomus*	1,125,000	Field data	Veith, et al. 1977
Redhorse sucker, *Moxostoma* sp.	32,000	Field data	Veith, 1975
White sucker, *Catostomus commersoni*	106,000	Field data	Veith, 1975
White sucker, *Catostomus commersoni*	5,500	30	Frederick, 1975

Table 6. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Channel catfish, Ictalurus punctatus	49,000	77	Stalling, 1971
Burbot, Lota lota	1,162,500	Field data	Veith, et al. 1977
Rock bass, Ambloplites rupestris	117,000	Field data	Nadeau & Davis, 1976
Bluegill, Lepomis macrochirus	52,000	77	Stalling, 1971
Largemouth bass, Micropterus salmoides	3,500	Field data	Martell, et al. 1975
Yellow perch, Perca flavescens	14,800	Field data	Hesse, 1973
Yellow perch, Perca flavescens	50,000	Field data	Hesse, 1973
Yellow perch, Perca flavescens	109,000	Field data	Veith, 1975
Yellow perch, Perca flavescens	154,000	Field data	Norstrom, et al. 1976
Slimy sculpin, Cottus cognatus	300,000	Field data	Veith, et al. 1977
Slimy sculpin, Cottus cognatus	84,000	Field data	Haile, et al. 1975
Fourhorn sculpin, Myoxocephalus quadricornis	337,500	Field data	Veith, et al. 1977

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Table 6. (Continued)

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Man	Edible fish and shellfish FDA action level	5	21 CFR Part 122.10
Mink, *Mustela vison*	Reduced reproduction	1	Ringer, et al. 1972
Mink, *Mustela vison*	No reproduction, mortality	0.64	Platonow & Karstad, 1973

Geometric mean fish bioconcentration factor = 427,000

Lowest residue concentration = 0.64 mg/kg

$\frac{0.64}{427,000}$ = 0.0000015 mg/kg or 0.0015 µg/l

Table 7. Other freshwater data for polychlorinated biphenyls

Organism	Test Duration	Effect	Result (µg/l)	Reference
Cladoceran, *Daphnia pulex*	4 days	Significant mortality	2,000 A-1242	Morgan, 1972
Cladoceran, *Daphnia magna*	2 wks	LC50	2.6 A-1248	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	2 wks	LC50	1.8 A-1254	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	3 wks	LC50	1.3 A-1254	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	2 wks	LC50	24 A-1254	Maki & Johnson, 1975
Ostracod, *Cypridopsis vidua*	3 days	Significant mortality	2,000 A-1242	Morgan, 1972
Glass shrimp, *Palaemonetes kadiakensis*	7 days	LC50	3 A-1254	Mayer, et al. 1977
Crayfish, *Orconectes nais*	7 days	LC50	30 A-1242	Mayer, et al. 1977
Dragonfly, *Macromia* sp.	7 days	LC50	800 A-1242	Mayer, et al. 1977
Midge, *Tanytarsus dissimilis*	3 wks	50% death of pupae	0.45 A-1254	Nebeker & Puglisi, 1974
Mosquito, *Culex tarsalis*	7 days	No adult emergence	1.5 A-1254	Sanders & Chandler, 1972
Rainbow trout, *Salmo gairdneri*	-	Inhibit ATPase activity	4 µg/g A-1242	Davis, et al. 1972
Rainbow trout, *Salmo gairdneri*	25 days	LC50	12 A-1242	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	25 days	LC50	3.4 A-1248	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	25 days	LC50	27 A-1254	Mayer, et al. 1977

Table 7. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Rainbow trout, Salmo gairdneri	25 days	LC50	49 A-1260	Mayer, et al. 1977
Rainbow trout, Salmo gairdneri	21 days	Induce fish hepatic microsomal enzymes	31 µg/g Clophen A-50	Lidman, et al. 1976
Rainbow trout, Salmo gairdneri	30 days	75% mortality, 70% deformed fry	0.39 µg/g PCB	Hogan & Brauhn, 1975
Rainbow trout, Salmo gairdneri	330 days	Kidney pathology	10 µg/g A-1254	Nestel & Budd, 1974
Rainbow trout, Salmo gairdneri	5 days	LC50	67 A-1242	Mayer, et al. 1977
Rainbow trout, Salmo gairdneri	5 days	LC50	54 A-1254	Mayer, et al. 1977
Steelhead trout, Salmo gairdneri	24 days	Bioconcentration factor	38,000 times	Halter, 1974
Coho salmon, Oncorhynchus kisutch	embryo-larval	MATC	<4.4	Halter & Johnson, 1974
Coho salmon, Oncorhynchus kisutch	72 hrs	Stimulated thyroid activity	0.48 µg/g A-1254	Mayer, et al. 1977
Coho salmon, Oncorhynchus kisutch	68 days	Induced fish hepatic AHH microsomal enzymes	1 µg/g A-1242	Gruger, et al. 1977
Coho salmon, Oncorhynchus kisutch	72 days	Induction of aryl hydrocarbon hydroxylase	12 µg/g PCB's	Gruger, et al. 1976
Atlantic salmon, Salmo salar	96 hrs	Bioconcentration factor	600 times	Zitko & Carlson, 1977
Atlantic salmon, Salmo salar	192 hrs	Mortality	>2 µg/g A-1254	Zitko, 1970

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Table 7. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Brook trout, Salvelinus fontinalis	embryo-larval	MATC	<0.43	Mauck, et al. In press
Brook trout, Salvelinus fontinalis	71 wks	No effect on survival growth or reproduction	0.94 A-1254	Snarski & Puglisi, 1976
Brook trout, Salvelinus fontinalis	fert. to hatch	No egg hatch	200 A-1254	Freeman & Idler, 1975
Brook trout, Salvelinus fontinalis	21 days	Stimulated hydroxylation of testosterone	200 A-1254	Freeman & Idler, 1975
Brook trout, Salvelinus fontinalis	21 days	Bioconcentration factor	164 times	Freeman & Idler, 1975
Brown trout, Salmo trutta	43 days	Anaemia hyperglycaemia altered cholestrol metabolism	10 µg/g in food Clophen A-50	Johansson, et al 1972
Northern pike (fry), Esox lucius	field data	Possible mortality	1.41 µg/g tissue 1.8 µg/g eggs A-1248	Waybrant, 1974
Carp, Cyprinus carpio	20 days	Altered plasma β-glucoronidase activity	5 µg/g A-1248	Ito, 1973
Carp, Cyprinus carpio	21 days	Metabolic changes	250 µg/g A-1248	Ito & Murata, 1974
Fathead minnow, Pimephales promelas	30 days	30-day LC50	28 A-1242	Veith, 1976
Fathead minnow, Pimephales promelas	30 days	-	28 A-1016	Veith, 1976
Fathead minnow, Pimephales promelas	30 days	Reduced growth	23 A-1016	Veith, 1976

Table 7. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Fathead minnow, Pimephales promelas	30 days	LC50	4.7 A-1248	DeFoe, et al. In press
Fathead minnow, Pimephales promelas	30 days	LC50	3.3 A-1260	DeFoe, et al. In press
Fathead minnow, Pimephales promelas	30 days	Significant mortality	23 A-1242	Hermanutz & Puglisi, 1976
Fathead minnow, Pimephales promelas	30 days	Significant mortality	44 A-1016	Hermanutz & Puglisi, 1976
Fathead minnow, Pimephales promelas	4 mos	Inhibition of ATPase activity	0.31 A-1242	Cutkomp, et al. 1972
Fathead minnow, Pimephales promelas	4 mos	Inhibition of APTase activity	0.31 A-1254	Koch, et al. 1972
Channel catfish, Ictalurus punctatus	30 days	LC50	75 A-1248	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	30 days	LC50	139 A-1254	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	30 days	LC50	433 A-1260	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	72 hrs	Stimulated thyroid activity	2.4 µg/g A-1254	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	30 days	LC50	8.7 A-1242	Mayer, et al. 1977
Channel catfish, Ictalurus punctatus	20 wks	Weight loss and liver hypertrophy	20 µg/g A-1242	Hansen, et al. 1976
Channel catfish, Ictalurus punctatus	2 wks	Increased transaminase, lower cortisol	8 A-1254	Camp, et al. 1974
Channel catfish, Ictalurus punctatus	4 wks	Induced fish hepatic microsomal enzymes	1,000 A-1254	Hill, et al. 1976

Table 7. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Flagfish, *Jordanella floridae*	30 days	Fin erosion	37 A-1242	Hermanutz & Puglisi, 1976
Mosquitofish, *Gambusia affinis*	6 days	Bioconcentration factor	12,100 times	Sanborn, 1974
Mosquitofish, *Gambusia affinis*	1.5 hr	Avoidance	0.1 A-1254	Hansen, et al. 1974
Guppy, *Poecilia formosa*	1 day	Significant mortality	200 A-1242	Morgan, 1972
Bluegill, *Lepomis macrochirus*	5 days	LC50	136 A-1248	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	--	Inhibit (I50) ATPase	0.6 µg/g A-1242	Desaiah, et al. 1972
Bluegill, *Lepomis macrochirus*	--	Inhibition of ATPase	30 A-1254	Yap, et al. 1971
Bluegill, *Lepomis macrochirus*	30 days	LC50	84 A-1242	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	30 days	LC50	78 A-1254	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	30 days	LC50	177 A-1254	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	30 days	LC50	400 A-1260	Mayer, et al. 1977
Mink, *Mustela vison*	--	Reduced reproduction	2 µg/g	Aulerich & Ringer, 1977
Mink, *Mustela vison*	1 yr	Depressed growth	10 µg/g	Aulerich, et al. 1973

Avoidance at 0.1 µg/l

SALTWATER ORGANISMS

Introduction

Polychlorinated biphenyls (PCB's) were manufactured by the direct chlorination of biphenyl; production in the United States has now ceased. These mixtures were identified under the trade name Aroclor and sold on the basis of percentage chlorine (e.g., 21, 42, 54, and 60 percent). Since each component of the mixtures differs in its physical, chemical, and biological properties, and since a possible 209 different chlorobiphenyls may be produced, the evaluation of the potential impact of the various mixtures on the environment is complicated.

When an evaluation of the impact of PCB's on the environment is performed, it is necessary to relate the data gathered in laboratory experiments with relatively pure mixtures to what happens to the mixtures in nature. There is evidence that percentages of chlorine change with time and location as the mixtures are transported through the environment. For example, the proportion of major peaks of Aroclor 1254 in shrimp and fish captured from Escambia Bay, Florida differed from each other (Nimmo et al., 1971). The major peaks in these organisms and in organisms from laboratory studies (Hansen et al., 1971) also differed from the standard used to calculate the amounts of the chemical in tissues. Results of environmental monitoring by Butler and Schutzmann (1978) showed that PCB's identified in fishes, Pacific staghorn sculpin and English sole from the Duwamish River, Washington State, during the period of fall 1972

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to spring 1976, changed from those resembling Aroclor 1254, to those resembling Aroclor 1260, and later, Aroclor 1242.

Acute Toxicity

Acute toxicity tests of PCB mixtures to saltwater fishes have not produced data that can be used to obtain 96-hour LC50 values because concentrations tested were not sufficiently high (Table 12). Pinfish were not affected in 48 hours by 100 µg Aroclor 1254 per liter of water (Duke et al., 1970). Eighteen percent of the pinfish died after 96 hours, compared to 2 percent of the control fish, in water to which 100 µg Aroclor/l was added (Hansen et al., 1974a). Additional tests with saltwater fishes at slightly higher concentrations might have given data necessary to calculate 96-hour LC50 values. However, possible problems could exist in validity of acute tests with PCB's because of their low solubility in water (Schoor, 1975).

Available data suggest that saltwater invertebrate species may be more acutely sensitive to PCB's than fishes (Table 8). The adjusted LC50 or EC50 values for invertebrate species ranged from 2.8 to 12.0 µg/l; an unusually low variability in adjusted LC50 values. Because there was little difference in the toxicity of different Aroclors, the geometric mean was calculated from all adjusted LC50 values and divided by the species senstivity factor of 49 to obtain a Final Invertebrate Acute Value of 0.14 µg/l. The narrow range in adjusted LC50 values suggests that (1) a species sensitivity factor of 49 is too great or (2) the more likely probability, based on freshwater invertebrate LC50 values is that not enough species have been tested to establish the variability in sensitivity of saltwater invertebrate species. Since there are too few data for PCB's and saltwater invertebrate species to calculate a specific species sensitivity factor, the guidelines value (49) is used. The Final Invertebrate Acute Value is used as the Final Acute Value because, although LC50 values are not available for fishes, they are not likely to produce a lower acute value.

Chronic Toxicity

No life-cycle tests have been reported using saltwater organisms. In an embryo-larval test (Table 9) with the sheepshead minnow, fertilization was not affected by Aroclor 1254, but significantly fewer embryos survived to hatching in a measured concentration of 3.48 μg/l (Schimmel et al., 1974). Survival of fish during the two weeks following hatching was significantly less in 0.16 μg/l but not different from controls in 0.06 μg/l.

In a second study to determine the effect of PCB's in fish eggs on survival, Hansen et al. (1973) exposed adult sheepshead minnows for four weeks to Aroclor 1254 (Table 12). Adult fish exposed to 5.6 μg/l died but those in 1.1 μg/l or lower apparently were not affected. Embryos from adult fish were placed in PCB-free flowing saltwater and observed for four weeks. Fertilization success was not affected by PCB's in eggs, but survival of embryos and the resulting fry was reduced. Fry from eggs containing 7.0 μg/g or more of PCB began dying a few hours after hatching. The concentration in eggs calculated to be lethal to 50 percent of the fish was 6.1 µg/g. If PCB affects other species similarly, then other fish species with equally high concentrations of Aroclor 1254 in their eggs may be endangered.

The effect of another PCB, Aroclor 1016, in water on fry, juvenile or adult sheepshead minnows was determined in a four-week exposure (Hansen et al., 1975). Survival of all three life-stages was reduced in 15 µg/l but not in 5.5 µg/l or less. Unlike Aroclor 1254, as much as 77 µg of Aroclor 1016/g of eggs apparently did not affect survival of embryos and fry in water free of this PCB.

Chronic exposure of fishes to Aroclor produced pathological effects not observed in acute tests. Hansen et al. (1971) reported signs of poisoning in pinfish exposed to Aroclor 1254, such as fungus-like lesions on the body, hemorrhagic areas around the mouth, ragged fins, etc. Signs of poisoning in sheepshead minnows exposed to Aroclor 1254 included lethargy, reduced feeding and fin rot (Hansen et al., 1973; Schimmel et al., 1974).

Spot exposed to Aroclor 1254 for two weeks or longer showed fatty changes in their livers (Nimmo et al., 1975). In intermediate stages of liver pathogenesis in fish exposed to Aroclor 1254, there were extreme fatty changes characterized by the presence of large vacuoles within hepatocytes and disorientation of liver cord distribution. In advanced stages of pathogenesis in a moribund fish, there were intracellular PAS-positive bodies (ceroid), congestion of blood sinuses, and severe vacuolation.

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Life-cycle tests with the fathead minnow and Aroclors 1242, 1248, 1254, and 1260 yielded Chronic Values of from 0.2 to 0.9 µg/l (Table 3). Degree of chlorination in these tests using a freshwater fish appears unrelated to extent of chronic toxicity and suggests that chronic data for all Aroclors be pooled when estimating a Final Fish Chronic Value.

The Fish Chronic Value for PCB's in salt water is the geometric mean of the chronic values (3.6 µg/l for Aroclor 1016, and 0.049 µg/l for Aroclor 1254) divided by the species sensitivity factor (6.7). The value thus obtained was 0.06 µg/l. This value is greater than the Final Fish Chronic Value of 0.049 µg/l obtained from the lowest chronic value.

No life-cycle tests have been reported in which saltwater invertebrate species were exposed to PCB's, however, several studies have shown that tests lasting longer than 96 hours provide a better estimate of adverse effects (mortality, growth, pathology) than lethality in 96-hour tests (Table 12). Aroclor 1254 killed pink shrimp at a concentration of 0.94 µg/l within 15 days (Nimmo et al., 1971). Pink shrimp exposed to 3.0 µg/l for 7 days were sensitive to changes in salinity (Nimmo and Bahner, 1974). This species also appeared more susceptible to a viral infection after exposure to Aroclor 1254 (Couch and Nimmo, 1974a; Couch and Nimmo, 1974b.

The growth rate (height and in-water weight) of Eastern oysters was significantly reduced exposed to 3.9 µg/l for 24 weeks (Lowe et al., 1972). These oysters also displayed general tissue alterations in the vesicular connective tissue (parenchyma) around the digestive diverticular of the hepatopancreas.

Aroclor 1254 was toxic to the saltwater amphipod, Gammarus oceanicus, at a nominal concentration of 10.0 µg/l (Wildish, 1970). Molting animals were particularly vulnerable to the PCB. Necrotic branchia were found in some animals exposed for about 6 days to a nominal concentration of 1.0 µg/l.

Aroclor 1254 affected the species composition of communities of estuarine animals that developed from planktonic larvae in salt water that flowed for four months through small aquaria (Table 12; Hansen, 1974). The number of arthropods decreased while the number of chordates increased in aquaria receiving 0.6 µg/l of the PCB. Numbers of phyla, species and individuals were decreased by this PCB, but there was no apparent effect on the abundance of annelids, brachiopods, coelenterates, echinoderms, or nemerteans. This study showed that a PCB can have marked effects on community structure at concentrations not much different from those that produced chronic effects on single species.

No Final Invertebrate Chronic Value can be obtained because no appropriate chronic tests on saltwater invertebrate species were found in the literature. However, extended exposures of saltwater species and life-cycle tests with freshwater invertebrate species (Table 4) demonstrate that acute tests underestimate the chronic toxicity of PCB's (Table 12). Therefore, knowledge of the chronic effects of this PCB are critical to the generation of a criterion.

Plant Effects

Information concerning the sensitivity of plants is restricted to unicellular algae (Table 10). Fisher and Wurster (1973) found that the growth of the diatom, Rhizosolenia setigera, was reduced in a medium to whch 0.1 µg/l Aroclor 1254 was added. Likewise, Fisher et al. (1974) demonstrated that 0.1 µg Aroclor 1254 added per liter of water changed the species ratio of the alga, Dunaliella tertiolecta, and the diatom, Thalassiosira pseudonana. Fisher et al. (1974) also showed a decrease in species diversity and species ratio change in natural phytoplankton communities at 0.1 µg/l Aroclor 1254. In summary, some data suggest that unicellular plants are affected by concentrations of PCB's similar to concentrations that are chronically toxic to animals. Unfortunately no data using measured concentrations were presented and it is difficult to interpret the ecological significance of these studies.

Bioconcentration

The bioconcentration factors (BCF's) of PCB's in saltwater species in laboratory tests are shown in Table 11. The diatom, Cylindrotheca closterium, had a bioconcentration factor of 1,000 (Keil et al., 1971); Eastern oyster, up to 168,000 times (Lowe et al., 1972); grass shrimp, Palaemonetes pugio, 42,000 times (Nimmo et al., 1974), and in the three fishes listed, Leiostomus xanthurus, Cyprinodon variegatus, and Lagodon rhomboides, as high

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as 44,000 times (Hansen et al., 1971; 1974a, and 1974b). Bioconcentration factors for PCB's in six of seven species of freshwater fishes in laboratory tests were generally similar, ranging from 5,000 to 60,000.

Bioconcentration factors calculated from data from Escambia Bay, Florida were greater than 230,000 for blue crabs (Nimmo et al., 1975), and greater than 100,000 for oysters, and 670,000 for speckled trout (Duke et al., 1970). These data, and field data on freshwater fishes, suggest that bioconcentration factors from laboratory studies underestimate bioconcentration potentials of PCB's in the environment (Hansen, 1975).

The bioaccumulation of PCB's into aquatic organisms from PCB's in food and in water and the effects of PCB's on mammals that feed on fish and shellfish are important. The lowest maximum permissible tissue concentration (0.64 µg/l) is based on the effect of dietary PCB's on mink (Platonow and Karstad, 1973). Using the geometric mean fish bioconcentration factor (27,000) a Residue Limited Toxicant Concentration of 0.024 µg/l is obtained. Effects on mink were seen at a dietary PCB concentration of 0.64 µg/g and a "no-effect" dose was not determined. A criterion calculated from these data may not be protective because the dietary concentration was not protective and the BCF based on laboratory studies may underestimate BCF's in saltwater animals since field-observed bioconcentration factors were higher but could not be used in the calculations. When field data were used for freshwater fish, a much higher BCF (427,000) was derived.

Miscellaneous

No other data exist that suggest any more sensitive effects (Table 12).

CRITERION FORMULATION

Saltwater Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 0.20 μg/l

Final Acute Value = 0.20 μg/l

Final Fish Chronic Value = 0.049 μg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 0.1 μg/l

Residue Limited Toxicant Concentration = 0.024 μg/l

Final Chronic Value = 0.024 μg/l

0.44 x Final Acute Value = 0.087 μg/l

The maximum concentration of polychlorinated biphenyls is the Final Acute Value of 0.20 μg/l and the 24-hour average concentration is the Final Chronic Value of 0.024 μg/l. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For polychlorinated biphenyls the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.024 μg/l as a 24-hour average and the concentration should not exceed 0.20 μg/l at any time.

Table 8. Marine invertebrate acute values for polychlorinated biphenyls

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Eastern oyster, Crassostrea virginica	FT	U	A-1016	96	10.2***	7.8	Hansen, et al. 1974a
Eastern oyster, Crassostrea virginica	FT	U	A-1248	24	17. ***	3.4	Lowe, undated
Eastern oyster, Crassostrea virginica	FT	U	A-1254	24	14.0***	2.8	Lowe, undated
Eastern oyster, Crassostrea virginica	FT	U	A-1260	24	60. ***	12.0	Lowe, undated
Brown shrimp, Penaeus aztecus	FT	U	A-1016	96	10.5	8.1	Hansen, et al. 1974a
Grass shrimp, Palaemonetes pugio	FT	U	A-1016	96	12.5	9.6	Hansen, et al. 1974a
Pink shrimp, Penaeus duorarum	FT	U	A-1248	48	32. ***	10.5	Lowe, undated
Pink shrimp, Penaeus duorarum	FT	U	A-1254	48	32.0***	10.5	Lowe, undated

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* FT = flow-through

** U = unmeasured

***EC50: Decreased growth of oysters; loss of equilibrium or death of shrimp.

Geometric mean of adjusted values = 9.67 µg/l $\frac{9.67}{49}$ = 0.20 µg/l

Table 9. Marine fish chronic values for polychlorinated biphenyls

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)	Reference
Sheepshead minnow, *Cyprinodon variegatus*	E-L	3.4-15.0**	3.6	Hansen, et al. 1975
Sheepshead minnow, *Cyprinodon variegatus*	E-L	0.06-0.16***	0.049	Schimmel, et al. 1974

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* E-L = embryo-larval test

** Aroclor 1016

***Aroclor 1254

Geometric mean = 0.42 µg/l $\frac{0.42}{6.7} = 0.060$ µg/l

Lowest chronic value = 0.049 µg/l

Table 10. Marine plant effects for polychlorinated biphenyls

Organism	Effect	Concentration (ug/l)	Reference
Diatom, Rhizosolenia setigera	No growth in 48 hr. Reduced growth thereafter	0.1*	Fisher & Wurster, 1973
Diatom, Thalassiosira pseudonana	Reduced growth	25-100*	Mosser, et al. 1972a
Diatom, Skeletonema costatum	Reduced growth	10*	Mosser, et al. 1972a
Diatoms, Thalassiosira pseudonana/ Skeletonema costatum	Reduced growth and carbon fixation in 48 hr	10*	Fisher, 1975
Diatom, Cylindrotheca closterium	Reduced growth	100**	Keil, et al. 1971
Phytoplankton populations	Toxicity in 24 hr	15*, 6.5**	Moore & Harriss, 1972
Green alga, Dunaliella tertiolecta/ Diatom Thalassiosira pseudonana (mixed culture)	Species ratio change	1*	Mosser, et al. 1972b
Green alga, Dunaliella tertiolecta/ Diatom Thalassiosira pseudonana (mixed culture)	Species ratio change	0.1*	Fisher, et al. 1974
Natural phytoplankton community	Decrease in species diversity, species ratio change	0.1*	Fisher, et al. 1974
Alga, Dunaliella tertiolecta	Reduction in rate of carbon fixation	100*	Luard, 1973

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* Aroclor 1254
** Aroclor 1242
Lowest plant value = 0.1 µg/l

Table 11. Marine residues for polychlorinated biphenyls

Organism	Bioconcentration Factor	Time (days)	Reference
Diatom, Cylindrotheca closterium	1,000*	14	Keil, et al. 1971
Eastern oyster, Crassostrea virginica	13,000**	84	Parrish, et al. 1974
Eastern oyster, Crassostrea virginica	101,000***	245	Lowe, et al. 1972
Eastern oyster, Crassostrea virginica	>100,000*****	Field data	Duke, et al. 1970
Grass shrimp, Palaemonetes pugio	27,000***	16	Nimmo, et al. 1974
Blue crab, Callinectes sapidus	>230,000*****	Field data	Nimmo, et al. 1975
Spot, Leiostomus xanthurus	37,000***	28	Hansen, et al. 1971
Sheepshead minnow, Cyprinodon variegatus	30,000***	28	Hansen, et al. 1973
Pinfish, Lagodon rhomboides	17,000*	21-28	Hansen, et al. 1974a
Speckled trout, Cynoscion nebrelosus	>670,000*****	Field data	Duke, et al. 1970
Fishes	>133,000****	Field data	Nimmo, et al. 1975
Invertebrates	>27,000****	Field data	Nimmo, et al. 1975

* Aroclor 1242

** Aroclor 1016

*** Aroclor 1254

**** Averages from field data from Escambia Bay, Fl., based on 27 water samples, 101 invertebrate samples, and 17 fish samples expressed as Aroclor 1254.

***** Greatest bioconcentration factor of Aroclor 1254 in mollusks, crustaceans, or fishes from Escambia Bay, Florida.

Table 11 (continued)

Organism	Bioconcentration Factor	Time (days)	Reference

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Man	Edible fish and shellfish FDA action level	5	21 CFR Part 122.10
Mink	Reduced reproduction	1	Ringer, et al. 1972
Mink	No reproduction, mortality	0.64	Platonow & Karstad, 1973

Geometric mean fish bioconcentration factor = 27,000

Lowest residue concentration = 0.64 µg/g

$\frac{0.64}{27,000}$ = 0.000024 mg/kg or 0.024 µg/l

Table 12. Other marine data for polychlorinated biphenyls

Organism	Test Duration	Effect	Result (ug/l)	Reference
Ciliate protozoans, *Tetrahymena pyriformis*	7 days	Bioconcentration factor = 60*	-	Cooley, et al. 1972
Ciliate protozoan, *Tetrahymena pyriformis*	96 hrs	Reduced growth	1000.**	Cooley, et al. 1973
Ciliate protozoan, *Tetrahymena pyriformis*	96 hrs	Reduced growth	1.0*	Cooley, et al. 1972
Ciliate protozoan, *Tetrahymena pyriformis*	96 hrs	Reduced growth	1000.***	Cooley, et al., 1973
Eastern oysters, *Crassostrea virginica*	2 days	Bioconcentration factor = 8,100*	-	Duke, et al. 1970
Eastern oysters, *Crassostrea virginica*	24 wks	Reduced growth	5.0*	Lowe, et al. 1972
Horseshoe crab, *Limulus polyphemas*	96 days	Bioconcentration factor = 1,298****	-	Neff & Giam, 1977
Amphipod, *Gammarus oceanicus*	30 days	Mortality	>10.0* <100.0*	Wildish, 1970
Grass shrimp, *Palaemonetes pugio*	1 hr	Avoidance	10.0*	Hansen, et al. 1974b
Pink shrimp, *Penaeus duorarum*	15 days	51% mortality	0.94*	Nimmo, et al. 1971
Pink shrimp, *Penaeus duorarum*	15 days	LC50	1.0*	Nimmo & Bahner, 1976
Pink shrimp, *Penaeus duorarum*	2 days	Bioconcentration factor = 140*	-	Duke, et al. 1970
Fiddler crab, *Uca pugilator*	38 days	Inhibited molting*****	8.0*	Fingerman & Fingerman, 1977
Communities of organisms	4 mos	Affected composition	0.6*	Hansen, 1974
Spot, *Leiostomus xanthurus*	12 days	50% mortality	5.0*	Hansen, et al. 1971

Table 12. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Pinfish, *Lagodon rhomboides*	1 hr	Avoidance	10.0*	Hansen, et al. 1974b
Pinfish, *Lagodon rhomboides*	18 days	50% mortality	5.0*	Hansen, et al. 1971
Pinfish, *Lagodon rhomboides*	2 days	Bioconcentration factor = 980*	-	Duke, et al. 1970
Pinfish, *Lagodon rhomboides*	42 days	50% mortality	21.0****	Hansen, et al. 1974a
Sheepshead minnow, *Cyprinodon variegatus*	28 days	Affected reproduction******	0.14*	Hansen, et al. 1973

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* Aroclor 1254

** Aroclor 1248

*** Aroclor 1260

**** Aroclor 1016

*****Aroclor 1242

******Significantly affected hatching of eggs or the survival of fry from exposed adults.

POLYCHLORINATED BIPHENYLS

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PCBs

Mammalian Toxicology and Human Health Effects

SUMMARY

Polychlorinated biphenyls (PCBs) have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. They have become widely disseminated in the environment worldwide. Like many organochlorine pesticides, they are highly persistent and accumulate in food webs. Human exposure to PCBs has resulted largely from the consumption of contaminated food but also from inhalation and skin absorption in work environments. PCBs accumulate in the fatty tissues and skin of man and other mammals. Metabolism occurs by hydroxylation and dihydrodiol formation with arene oxides as probable intermediates. The rate of metabolism and excretion slows dramatically as the chlorination of the biphenyl nucleus increases. Arrangement of chlorines which eliminate adjacent unsubstituted carbons greatly increase resistance to metabolism. PCBs have caused profound toxic effects in man and animals, particularly if repeated exposures occur. The skin and liver are major sites of pathology with the gastrointestinal tract and nervous systems also being targets. Polychlorodibenzofurans which contaminate commercial PCB mixtures may contribute significantly to their toxicity. Several studies in rodents suggest strongly that some PCBs are carcinogenic and that they can enhance the carcinogenicity of other chemicals. A linear model for risk assessment has been used to estimate maximum safe levels in water and fish which will establish a level of risk for the human population from cancer. A maximum level of PCBs in water projected to result in no more than 1 cancer in 10^5 individuals with lifetime exposure of 0.26 ng/liter is suggested by the analysis.

EXPOSURE

Introduction

PCB's have become widespread in the environment since the introduction of their commercial use in 1929 (Peakall, 1975). The magnitude of the dispersal of these chemicals is revealed by their detection in the tissues of plants and animals in all parts of the world. PCB residues have been observed in wildlife in Sweden, North America, Great Britain, the Netherlands, and even the Arctic (Risebrough and de Lappe, 1972). Because PCBs are not naturally occurring substances, their dissemination is entirely the result of human activity. Their entry into the environment has occurred by vaporization into the atmosphere, and by spilling or dumping into water or onto land. It has been estimated that of the 1970 sales of PCBs in North America only 20 percent represented a net increase in the total amount in service. Estimated sources of loss for that year were 1 - 2 x 10^3 tons for evaporation; 4 - 5 x 10^3 tons for leaks and disposal of fluids; and 22 x 10^3tons from disposal by incineration and burial (Nisbet and Sarofim, 1972). The cumulative input to the environment between 1930 and 1970 was estimated to be 3 x 10^4 tons to air, 6 x 10^4tons to fresh and coastal waters, and 3 x 10^5 tons to dumps and landfills. In that time, up to 1/3 of the PCBs released to air and 1/2 of that released to water were probably degraded. Degradation in landfills is more difficult to estimate (Nisbet and Sarofim, 1972). PCBs have been found repeatedly to be widespread in analyses of human tissues. For example, detectable levels of PCBs have been reported in adipose tissue samples of up to 91 percent of individuals sampled in a survey of the United States population (Kutz and Strassman, 1976; see Table 12). This finding suggests that environmental contamination may be a significant source of human exposure. Likely routes of exposure for the general population are water and particularly food while inhalation and dermal contact are likely to be more significant routes in occupational exposure.

Ingestion from Water

The solubility of PCBs in water is very low, decreasing as the percent chlorination is raised. Solubilities of Aroclors in water at 20° vary from 200 μg/l for 1242 to about 25 μg/l for 1260 (Nisbet and Sarofim, 1972). The major factors in the dynamics of PCB distribution in water are its low solubility, high specific gravity, and its high affinity for solids. Most PCBs discharged into water are found in bottom sediments near the site of discharge (Nisbet and Sarofim, 1972). Evaluation of PCB levels in surface waters and bottom sediments of the major drainage basins of the United States was conducted between 1971 and 1974 (Dennis, 1976). The data were derived from the U.S. Geological Survey study of 1971-72 (Crump-Weisner, et al. 1974) and from additional data collected by the USGS between 1972 and 1975 (PCB data base 1972-75). It is summarized in detail in the Criteria Document for PCBs (U.S. EPA, 1976a). The highest concentrations in both water and sediment were found in the basins east of the Mississippi River. The highest levels were found in 1971 in the lower Mississippi basin with a median concentration for the region of 3 ug/l and positive detections at 100 percent of stations tested. Over the time period of the study the concentrations and incidences of PCBs detected in all basins have decreased substantially. By 1974 the median level in the lower Mississippi basin had dropped to 0.1 μg/l and the incidence of detection to 2.6 percent of stations tested. The levels in sediments however, have persisted at much higher levels over this period of time. In 1971 median sediment levels for the Mississippi basin were 30 μg/kg and the incidence of detection 100 percent. By 1974 the incidence had dropped to 9.9 percent and the median level was 10.5 μg/kg.

Although PCBs are widespread in aquatic environments (Peakall, 1975) their low solubility generally prevents them from reaching high concentrations in drinking water supplies. The persistence of PCBs and their accumulation in sediments increase the significance of water as a source of human exposure by providing a reservoir of material which can continue to contaminate water long after the addition of PCBs has ceased. In combination with these factors, the lipophilicity of PCBs results in their continued introduction to, and accumulation in, the food chain. As a consequence, fish and other foods obtained from aquatic environments may become important sources of exposure even if PCB levels in the water are low.

The ability of PCBs discharged from a manufacturing facility to contaminate a drinking water system has recently been highlighted. Billings, et al. (1978) determined the levels of PCBs in the Easley-Central Water District, Pickens County, South Carolina. They observed that PCBs discharged by a capacitor manufacturing facility 12 km upstream from the water district's treatment plant were entering the water system. Finished potable water supplies were contaminated to levels as high as 818 ng/l.

Ingestion from Foods

Contamination of food with PCBs occurs primarily by three mechanisms. The first is contamination of human food as a consequence of accumulation in the food chain. The contamination of freshwater fish as a consequence of the contamination of the aquatic environment is a particularly significant route of PCB entry into the human diet which will be discussed in more detail below. The second mechanism occurs by the direct contamination of feeds or foodstuffs with PCBs. This may occur as a result of accidental spills or equipment malfunctions as was the case in the episode of rice oil contamination in Japan which led to the outbreak of Yusho or rice oil disease in 1968 (Kuratsune, et al. 1976). In this instance leaks in a heat exchanger used to process rice bran oil resulted in the contamination of the oil by the exchanger fluid (Kanechlor 400). Discovery of the contamination was made only after numerous cases of chlorinated hydrocarbon intoxication in Fukuoka prefecture, Japan. The oil was found to contain 2,000 to 3,000 ppm Kanechlor 400 which was contaminated with polychlorodibenzofurans (1.6 to 5 ppm). Average consumption of PCBs among affected individuals was estimated to be 2 g (Kuratsune, et al. 1972). By 1975 the total number of known individuals affected was 1,291. Elevated PCB levels in fat were still observed four years after the exposure, and dermatological symptoms were found in up to 89 percent of a group of 72 patients examined in 1973 or 1974. Another example of accidental PCBs contamination in animal feed occurred as a result of the use of PCBs in silo coatings (Willett and Hess, 1975). The third significant source of PCBs in foodstuffs was food packaging made from recycled paper containing PCBs (Jelinek and Corneliussen, 1976).

A special case of human exposure via food which must be considered is human breast milk. Adverse effects have been observed in breast fed infants of women with Yusho (Kuratsune, et al. 1976) and in infant Rhesus monkeys ingesting breast milk containing 7 to 16 ppm PCBs (fat basis) (Allen, 1975; Allen and Barsotti, 1976). Preliminary survey data indicate average PCB levels in human breast milk of 1.8 ppm (fat basis) (42 FR 17487) and a study of PCB exposed nursing mothers in Germany indicated average PCB levels of 3.5 ppm (Tombergs, 1972). The proximity of these values to the toxic levels in infant monkeys (7 to 16 ppm) suggests that human breast milk must be considered a significant source of PCB exposure.

The extent of contamination of the U.S. food supply has been the subject of Food and Drug Administration (FDA) and Department of Agriculture (USDA) monitoring programs since 1969. Results of these studies have been summarized by Jelinek and Cornelliussen (1976). The initial analysis of 15,000 food samples between 1969 and 1971 is summarized in Table 1. The results of monitoring programs in fiscal years 1973, 1974, and 1975 are summarized in Table 2. Over the monitored period the incidence and levels of PCBs have dropped in all food classes. By 1975 the only significant food sources were fish, meat, and dairy products. Fish were

TABLE 1

Summary of PCB's in Food
Nov., 1969 - June, 1971[a]

Food commodity	Positive findings[c]	Avg. of positives (ppm)	Max. level (ppm)
Finfish	317	2.1	35.3
Oysters	12	Trace	Trace
Fish byproducts	6	1.8	5.0
Cheese	44	0.3[b]	1.0[b]
Milk	60	2.5[b]	22.8[b]
Eggs	17	Trace	0.5
Potato byproducts	12	1.1	4.2
Miscellaneous	11	1.9	6.5

[a] Approximately 15,000 samples examined.

[b] Fat basis.

[c] Detection limits: fish 0.5 ppm, other foods 0.05 ppm (P.E. Corneliussen personal communication).

From: Jelinek and Corneliussen (1976).

TABLE 2

Summary of PCBs in Foods. FY73, 74 and 75

	FY '73		FY '74		FY '75	
Food Commodity	Percent positive[b]	Max. (ppm)[a]	Percent positive	Max. (ppm)[a]	Percent positive	Max. (ppm)[a]
Fish	60.4	123.0	44.0	16.8	17.8	9.0
Milk	2.2	1.6	2.6	2.3	0.7	1.9
Eggs	1.1	Trace	4.2	11.0	0.0	N.D.
Cheese	0.9	0.5	2.6	2.8	0.0	N.D.
Feed components	12.7	9.0	0.0	N.D.	0.3	0.9
Animal feeds	7.2	199.5	0.0	N.D.	0.0	N.D.
Processed fruits	4.5	19.2	0.0	N.D.	0.0	N.D.
Infant & jr. foods	1.1	Trace	0.0	N.D.	0.0	N.D.
	Percent positive	Percent above 5 ppm[a]	Percent positive	Percent above 5 ppm[a]	Percent positive	Percen above 5 ppm
Meats & poultry (USDA)	1.9	0.19	1.2	0.07	0.3	0.06

[a] Milk, cheese, meats and poultry reported as ppm, fat basis.

[b] Detection limits: fish 0.5 ppm, other foods 0.05 ppm. (P.E. Corneliussen, personal communication).

From: Jelinek and Corneliussen (1976).

by far the most significant source. The findings for the 1969-71 period led to the establishment of regulations for PCB levels in food (38 FR 18096). The temporary tolerances established at that time and new tolerances recommended in 1977 (42 FR 17487) are given in Table 3. The enforcement of those tolerances and restriction of PCB use in open systems after 1970 probably account for the general decline of PCB levels in foodstuffs.

Comprehensive fish surveys conducted by the FDA in fiscal years 1973 and 1974 indicated a drop in the incidence of PCB detection in fish from less than 30 percent in 1973 to less than 20 percent in 1974. In 1973 three percent contained over 1 ppm and 0.5 percent contained over 5 ppm PCBs. The data from all FDA studies in the fiscal years 1973, 1974, and 1975 are summarized in Figure 1. While the incidence of PCBs in fish dropped over the period the fraction of positive fish containing over 5 ppm PCBs increased from less than five percent to over ten percent. The samples containing more than 5 ppm were from the Great Lakes. Because the study involved different sources and objectives from year to year no conclusion as to whether a significant trend existed was drawn. It should be noted that these surveys were conducted with fish in commerce and provide no information about sport fish per se. The studies indicated that significant levels of PCBs generally do not occur in salt water fish.

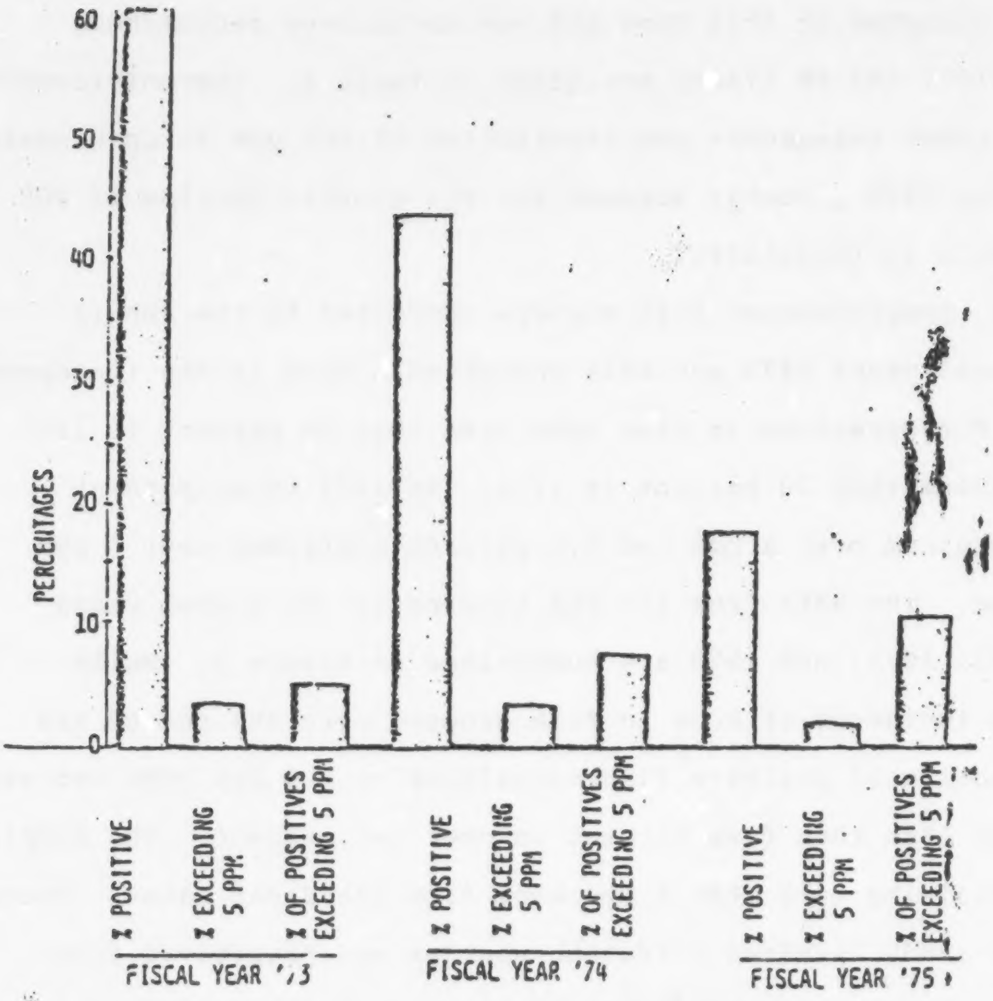


Figure 1: PCBs in fish FY73, 74, 75 a level of detection: 0.5 ppm.

From: Jelinek and Corneliussen (1976).

TABLE 3

FDA Regulations for PCBs

I. Temporary tolerances

Commodity	PCB conc. (ppm)	Proposed Guidelines 1977
Milk (fat basis)	2.5	1.5
Dairy products (fat basis)	2.5	1.5
Poultry (fat basis)	5.0	3.0
Eggs	0.5	0.3
Finished animal feed	0.2	0.2
Animal feed components	2.0	2.0
Fish (edible portion)	5.0	2.0
Infant and junior foods	0.2	pending
Paper food-packaging material without PCB-impermeable barrier	10.0[a]	

II. Use prohibited in food, feed, food packaging plants

[a] Administrative guideline, pending hearing.

From: Jelinek and Corneliussen (1976)
42 FR 17487

The impact of sport fish consumption was examined in a study of a group of sports fishermen who consumed an average of 24 to 25 pounds of fish annually (highest individual exposure 180 lbs/year over a two-year period). PCB residues in cooked fish ranged from 0.35 - 5.38 ppm. Plasma PCB levels ranged from a high of 0.366 ppm in the exposed group to control levels 0.007 ppm (less than six lbs consumed per year) (42 FR 17487).

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

Measured bioconcentration factors were obtained in tests lasting over 200 days with three species using Aroclor 1242, 1248, 1254, and 1260:

Organism	Average BCF	Percent lipids	Adjusted BCF	Reference
Brook trout *Salvelinus fontinalis*				Snarski & Puglisis, 1976
fillets, A-1254	2,800	0.65	9,900	
whole body, A-1254	12,000	2.8	9,900	
Fathead minnow *Pimephales promelas*				DeFoe, et al. 1978
females, A-1248	240,000	10.4	53,000	
males, A-1248	120,000	4.2	66,000	
males, A-1260	270,000	3.3	188,000	
females, A-1260	540,000	9.7	128,000	
Fathead minnow *Pimephales promelas*				Nebeker, et al. 1974
males, A-1242	123,000	3.8	74,000	
females, A-1242	75,000	10.0	17,000	
males, A-1254	181,000	3.8	109,000	
females, A-1254	283,000	10.0	49,000	

Eastern oyster *Crassostrea virginica*				Lowe, et al. 1972
A-1254	93,000	1.5	142,000	

Only tests lasting over 200 days were used since long exposures are necessary to reach steady-state. The percent lipids for mature fathead minnows were obtained from DeFoe, et al. (Personal communication). The percent lipids for oysters was obtained from Sidwell, et al. 1974. Each of these average measured BCF's was adjusted from the percent lipids of the test species to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. The geometric mean was obtained for each species, and then for all species. Thus, the weighted average bioconcentration factor for PCB's and the edible portion of all aquatic organisms consumed by Americans is calculated to be 46,000.

Higher BCF values apparently can be achieved in field exposures (Haile, et al. 1975; Norstrom, et al. 1976; Duke, et al. 1970; Nimmo et al. 1975; Veith, 1975; Veith, et al. 1977), but those values cannot be considered quantitative because the exposure of the organism cannot be adequately documented and integrated over a long enough period of time.

In order to estimate human dietary PCB intake the FDA conducts a continuing survey of the total diet. Composites of 12 different food categories are analyzed for PCB content. Table 4 summarizes the results of the survey from 1971 through the first half of 1975. While contamination was observed in most categories in 1972 the number of positive categories had dropped by 1973. In 1974 and 1975 only meat, fish, and poultry were observed to contain PCBs and fish was almost

TABLE 4

Percent of Composites Containing PCBs, From the FDA Total Diet Studies

Fiscal Year	Dairy Products	Meat, Fish & Poultry	Gran and Cereal Prods.	Potatoes	Legume Vegetables	Root Vegetables	Garden Fruits	Oils, fats & Shortening	Sugars and Adjuncts
1971		47	13						
1972	6	46	6		6	3	3	17	6
1973	10	33	17	3				3	
1974		43							3
1975 (1st half)		40							

From: Jelinek and Corneliussen. 1976.

always the contributor of positive results in that category (Jelinek and Corneliussen, 1976). Most of the contamination noted in the other categories in earlier years was thought to result from exposure during processing or packaging because the raw foods were rarely found to contain PCBs. Total daily intake, calculated from the composite figures for a young adult male over the period 1971-1975, is summarized in Table 5. Total daily intake dropped by almost 50 percent over the period but intake in the meat-fish-poultry category changed very little. By 1974 almost all of the dietary intake resulted from the ingestion of PCB-contaminated fish. The measures taken in the early 1970's to limit the release of PCBs into the environment and to remove them from food processing environments effectively reduced direct contamination of foodstuffs to a minimum level. The persistence of PCBs in aquatic environments and in fish has maintained a residual dietary exposure level in the diet. Further reduction of PCB levels in the diet will require that entry of PCBs into waterways be more tightly controlled and that monitoring of fish and other foods for PCB contamination be continued (Jelinek and Corneliussen, 1976). The recently recommended reduction of allowable PCB levels in fish to 2.0 ppm may further reduce dietary intake (42 FR 17487).

Two special situations should be mentioned which must be avoided to prevent unnecessary PCB ingestion. First, accidental contamination of foodstuffs or feeds with PCBs must be avoided. Although PCB manufacture is now stopping

TABLE 5

Estimates of daily PCB intakes (Total Diet Study - Teenage Male)

Fiscal year	Average daily intake of PCB's[a] Total diet (μg/day)	 Meat-fish-poultry food class (μg/day)
1971	15.0	9.5
1972	12.6	9.1
1973	13.1	8.7
1974	8.8	8.8
1975 (1st half)	8.7	8.7

[a] Lower limit of quantitative reporting = 0.05 ppm with analytical method employed.

From: Jelinek and Corneliussen (1976)

and distribution will cease in the near future, many PCB containing products remain in service. Failure to exercise care in the maintenance and disposal of these units could result in the contamination of food or water. The tragic results of the episode of rice oil contamination in Japan (Kuratsune, 1972) provides ample evidence of the need for care and continued surveillance of foods. Second, although occupational exposure to PCBs will decline over the next several years, the possibility of food contamination as a consequence of transfer from workers tools' or clothing must be considered as a possible route of dietary exposure.

Inhalation

PCBs can enter the atmosphere by vaporization and may be found in either gaseous form or adsorbed to airborne particulates. Prior to the restriction of PCB use, substantial losses to the atmosphere resulted from evaporation of plasticizers and from improper incineration (Nisbet and Sarofim, 1972). In 1972 terrestrial input from fallout was estimated to be 1000 to 2000 tons/year. Annual emission rates were estimated at 1500 to 2500 tons (Nisbet and Sarofim, 1972). In 1975 a study of PCB content in air in suburban areas in Florida and Colorado indicated that average atmospheric levels were approximately 100 ng/m^3 (Kutz and Yang, 1976). Rates of fallout along the southern California Coast were estimated to average 1800 kg/year over a 50,000 km^2 area (Young, et al. 1976). The distribution of PCBs in air is non-uniform, being more highly concentrated in urban areas. The aerial fallout survey in southern California indicated that sectors in the urban areas around Los Angeles had fallout rates of up to 180 kg/yr while less industrialized sectors had rates as low as 30 kg/yr. A study of PCB levels in soil samples showed that they were rarely detectable in agricultural soils but were found in 63 percent of urban samples from 19 cities (Carey and Gowan, 1976). General human exposure to inhaled PCBs probably varies with the local conditions. Relative to the 9 μg/day intake estimated from the diet (Jelenek and Corneliussen, 1976) non-occupational exposures by inhalation are probably small.

While inhalation of PCBs is not and most likely will not be a major route of general human exposure, it is a highly significant route of occupational exposure. Early in its commercial use an association was observed between occupational exposure to PCB vapors and chloracne (Jones and Alden, 1936; Schwartz, 1936). The benefits of controlling leaks from closed systems into work environments were noted by Meigs, et al. (1954).

A study of occupational exposure in Japan found PCB vapors at levels between 13 and 540 $\mu g/m^3$ and airborne particulates between 4 and 650 $\mu g/m^3$ in a survey of six industrial plants. An additional finding of 6,270 $\mu g/m^3$ PCB particulates was associated with a spill. Blood PCB levels of 99 exposed workers averaged 370 ppb as compared to levels in 32 controls of 20 ppb (Hasegawa, et al. 1972). Ouw, et al. (1976) observed Aroclor 1242 levels between 2.22 and 0.32 mg/m^3 in different areas of an electrical equipment manufacturing facility in Australia. Blood Aroclor levels were analyzed by gas chromatography and fractions with several retention times standardized against Aldrin were detected in exposed workers. Workers in an impregnation room where inhalation was a major mode of exposure had higher levels of PCBs than did workers in another area where exposure was primarily dermal. A series of 30 control individuals were not found to have detectable PCB levels. The limit of detection in this study was not reported; however, Finklea, et al. (1972) reports American control population blood levels of 0.3 to 3 ppb.

It is difficult to differentiate between industrial exposure by inhalation and dermal absorption (see below). Animal studies do indicate that animals exposed to PCB aerosols show rapid increases in liver PCB levels. Exposure to Pydranl A 200 for 15 minutes resulted in the accumulation in the liver of 50 percent of the PCBs accumulated after two hours (Benthe, et al. 1972). The lung appears to be a good site of absorption and certain occupational environments contain significant levels of airborne PCBs. The National Institute of Occupational Safety and Health has recently proposed an occupational exposure limit of 1.0 $\mu g/m^3$ on a time weighted average 10-hour day, 40-hour week basis (Natl. Inst. Occup. Safety Health, 1977). Assuming a tidal air volume of 10 m^3 in an eight-hour day and 100 percent absorption, the resulting dose at this exposure level would be 10 μg/day.

Dermal

Dermal exposure, like inhalation exposure, is a particularly significant route in the occupational setting. With the restriction of PCB uses to sealed systems, the use of PCBs in products to which the public might be exposed has declined markedly, reducing opportunities for general exposure. Past uses of PCBs in carbonless copy paper, printers inks, and other products probably contributed to general PCB exposures. Documented exposures are largely occupational as exemplified by the results of Ouw, et al. (1976). The authors noted that one group of employees were largely exposed through skin contact and had significantly elevated blood PCB levels.

In a variety of animal studies dermal application of several PCB containing materials has produced both local and systemic effects including liver degeneration and death (Miller, 1944; Paribok, 1954; Vos and Beems, 1971). In neonatal rats treated by skin application with PCBs, a five- to ten-fold increase in aryl hydrocarbonhydroxylase activity occurred in liver, skin, lung, and kidney, indicating significant distribution to these tissues after exposure by this route (Bickers, 1976; Bickers, et al. 1975).

The relative contributions of various routes of exposure can be expected to vary widely. Occupational exposures are by far the most severe with inhalation and skin contact being the major routes of absorption. A noteworthy by-product of occupational PCB exposure is the elevated risk of exposure among other members of workers' families. An epidemiological study in Bloomington, Indiana revealed significantly elevated serum PCB levels among a group of 18 occupationally exposed workers (mean 71.7 ppb) and a slight elevation among 19 members of their families (near 33.6 ppb) as compared to background levels (5 to 20 ppb) (McCloskey, et al. 1978). The general public is widely exposed to PCBs but at much lower levels and primarily through the diet. Fish living in contaminated waters are by far the largest contributors to dietary PCBs (Jelinek and Corneliussen, 1976).

PHARMACOKINETICS

Absorption

The efficiency of PCB absorption in the gut of rats was shown to be between 92 to 98.9 percent, (Albro and Fishbein, 1972). Neither degree of chlorination (mono-hexachlorobiphenyl) nor the dose ingested (5 to 100 mg/kg) markedly affected the efficiency of uptake. Matthews and Anderson (1975b) observed a reduced accumulation of PCBs in adipose tissues of rats exposed orally as compared to i.v. injection. The differences were more pronounced with biphenyls of low chlorine content and were thought to be related to route of absorption and metabolic rates, rather than to the overall efficiency of transport across the gut. Absorption via the gut was also very efficient in adult Rhesus monkeys, 90 percent of a single dose of 1.5 or 3.0 g/kg Aroclor 1248 being absorbed from the gastrointestinal tract (Allen, et al. 1974).

Efficient absorption via inhalation has been demonstrated in rats by Benthe, et al. (1972).

In humans, absorption via the intestine has been best illustrated by the "Yusho" incident in Japan in 1968. Among individuals ingesting less than 720 ml of contaminated rice bran oil (equivalent to 1.5 to 2.2 g Kanechlor 400) 39 percent developed severe symptoms and an additional 49 percent developed moderate symptoms of PCB intoxication. The lowest level of PCB ingestion in an affected [illegible] was estimated to be 0.5 g (Kuratsune, et al. 1972). [illegible] via the respiratory tract and skin is also [illegible] indicated by occupational exposures where effects [illegible] exposure can be detected even at doses too [illegible] pathology (Alvares, et al. 1977).

Distribution

PCBs given to rats by i.v. [illegible] from the blood rapidly and stored initia[illegible] liver and muscle. With time they are redistributed primarily to skin and adipose tissue (Matthews and Anderson, 1975b). The degree to which PCB's are stored or excreted depends on their susceptibility to metabolism and, therefore, on the degree of chlorination and availability of adjacent unsubstituted carbons. Tissue levels of mono-, di-, penta- and hexachloro-biphenyls in rats given a single injected dose at 0.6 mg/kg were determined by Matthews and Anderson (1975b). The maximum doses accumulated in each tissue increased with degree of chlorination as did the half life in each tissue. The proportion of total PCBs present in tissues as metabolites was greatest for the mono-and di-chlorobiphenyls. Hexachlorobiphenyls in tissues were largely unmetabolized. The distribution of PCBs in adipose tissue provides a useful example of the relative accumulation of different isomers. Tissues were examined for up to 42 days and a summary of the results is presented in Table 6.

TABLE 6

Storage of PCBs in Adipose Tissue in Rats (Values are Percent of Total Dose 0.6 mg/kg)

Degree of Chlorination	Maximum	Time of Maximum Stored	Amount at 7 Days
mono-	11.63 ± 5.64	1 hr	0.234 ± 0.055
di-	52.75 ± 14.99	2 hr	1.837 ± 0.213
penta-	23.54 ± 3.0	1 day	13.04 ± 2.1
hexa-	85.18 ± 21.6	42 days	56.08 ± 15.72

Adapted from Matthews and Anderson, 1975b.

A similar pattern was observed in skin with up to 22 percent of the hexachlorobiphenyl dose being accumulated there at 1 day and residual levels around 15 percent remaining at 42 days.

Single intravenous doses of 0.6 or 6.0 mg/kg 2, 4, 5, 2', 5' pentachlorobiphenyl were cleared from the blood in ten minutes and initially deposited in liver and muscle. They were subsequently translocated to adipose tissue and skin as depositories (Matthews and Anderson, 1975a).

A single administration of approximately 500 mg/kg 2, 5, 2', 5' tetrachlorobiphenyl to rats resulted in a similar distribution with adipose, skin, and blood being the significant storage depots after 24 hours (Van Miller, et al. 1975).

The significance of chlorine position as well as number was addressed in a study of the pharmacokinetics of 3, 5, 3',5' tetrachlorobiphenyl (TCB) by Tuey and Matthews (1977). The arrangement of chlorines on this molecule results in the absence of adjacent unsubstituted sites. The pattern of distribution of the compound following a single i.v. injection of 0.6 mg/kg was similar to that observed in earlier studies (Matthews and Anderson, 1975a,b) with adipose tissue and skin becoming the major long term storage sites. However, loss of 3, 5, 3',5' TCB was slower than earlier observed for 2, 4, 5, 2', 5' pentachlorobiphenyl (see penta CB Table 6) with the maximum adipose tissue load reaching 52.9 percent of total dose on day four and the residual on day seven remaining at 45.4 percent. The distribution of several tetrachlorobiphenyl isomers in mice was analyzed by Mizutani, et al. (1977). In all cases the accumulation of the compound was greater in the carcass than in the liver. A tendency for those isomers with adjacent unsubstituted carbons to be rapidly cleared was observed. 2, 6, 2', 6' TCB was very rapidly cleared from carcass and liver, and 2, 3, 2',3' TCB was cleared fairly rapidly. However, 2, 4, 2', 4' TCB was more resistant to removal than 3, 5, 3', 5' TCB which might not be anticipated on structural grounds. The half life in the carcass of the former was 9.2 days but only 2.1 days for the latter. The degree of accumulation of the isomers was assessed by the introduction of an index referred to as a storage ratio (the daily amount entering storage/daily oral ingestion). By this measure 3, 5, 3', 5' TCB and 2, 4, 2',4' TCB were similar with indices of 0.7 and 0.6, respectively, while the more readily metabolized 2, 3, 2', 3' TCB had an index of 0.06.

The distribution of 2, 5, 2', 5' TCB in infant Rhesus monkeys was determined after a single dose of tritiated TCB (500 mg/kg). At 72 hours the distribution differed from that in rats in that the label was more widely dispersed in the monkeys. Blood levels were lower than observed in rats and the major storage depots were bone marrow, adrenal and skin. Most of the labelled material was associated with macromolecules although it was largely extractable and not covalently bound (Hsu, et al. 1975a).

Distribution of PCBs in the human body has not been the subject of systematic experimentation. Data available from general population surveys indicate that general patterns of distribution are consistent with those found in other animals. When detected in the adipose tissue of the general populace, PCB levels are around 1 mg/kg (Yobs, 1972; Kutz and Strassman, 1976; and Grant, et al. 1976). Plasma levels detected in the general populace are two to three orders of magnitude lower than adipose levels (Finklea, et al. 1972) Similarly, Yusho patients exhibited a 100 to 1000 fold greater concentration in the fat of skin, liver and in adipose tissue than in plasma. Over several years both the fat and plasma levels were observed to decline to near normal levels (Kuratsune, et al. 1976). The PCBs found in human adipose tissues in the U.S. chromatographically resemble Aroclor 1254 and 1260, suggesting that less chlorinated isomers found in Aroclor 1248 are preferentially excreted (Kutz and Strassman, 1976).

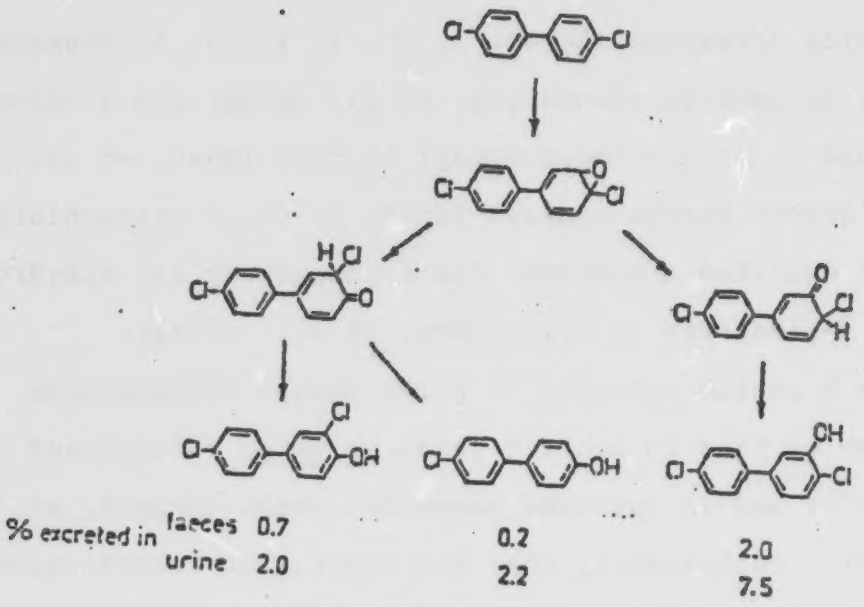
Metabolism

The metabolism of PCBs has been studied extensively in several organisms. A detailed review of PCB metabolism was written by Sundstrom, et al. (1976a). Rather than attempt to treat the subject exhaustively this section will summarize the major characteristics of PCB metabolism which relate to their distribution, accumulation, toxicity, and possible mechanisms of carcinogenicity.

The metabolism of PCBs depends on their chlorine content, and the sites of chlorination on the biphenyl (Sundstrom, et al. 1976a; Lutz, et al. 1977). While the overall mechanisms of metabolism appear to be similar in most vertebrates examined, the capacity to metabolize PCBs declines from mammals to birds to fish (Hutzinger, et al. 1972). Elucidation of PCB metabolism has been made possible by the use of individual purified isomers. Predominantly, the products of PCB metabolism at all levels of chlorination are biphenylols, biphenyldiols, and dihydrodihydroxybiphenyls, although the types and proportions of specific metabolites vary in different species. A few biphenyltriols and methoxy derivatives have also been observed (Sundstrom, et al. 1976a).

The structures of several PCB metabolites support the formation of arene oxides as intermediates. The first evidence for the formation of arene oxide intermediates was obtained by Gardener, et al. (1973). They isolated trans 3, 4 dihydroxy-3, 4-dihydro-2, 2', 5, 5' tetrachlorobiphenyl as a metabolite of 2, 2', 5, 5' tetrachlorobiphenyl in rabbits. More direct evidence for the formation of arene oxides was obtained by Safe, et al. (1975, 1976). In rabbits and frogs the biohydroxylation of 4-chlorobiphenyl was investigated using 4'-^{2}H-4-chlorobiphenyl. The major metabolite 4' chloro-4-biphenylol retained 79 percent of the label which is consistent with arene oxide formation (Daly, et al. 1972). The subsequent isomerization of the arene oxide results in the migration of the deuterium atom from the ultimate site of hydroxylation to the adjacent carbon, an NIH shift. Daly, et al. (1972) consider the NIH shift of labeled hydrogens, halogens or alkyl substituents to be indicative of enzymatic arene oxide formation. A subsequent hydroxylation to 4'chloro-3, 4-biphenyldiol resulted in the loss of half the remaining deuterium suggesting a direct hydroxylation rather than a second arene oxide formation (Safe, et al. 1975). 4, 4'-dichlorobiphenyl produced three metabolites in the rabbit: 4, 4'-dichloro- 3-biphenylol, 3, 4'-dichloro - 4-biphenylol and 4'-chloro-4-biphenylol. These products are consistent with a mechanism involving 3, 4-arene oxide formation followed by epoxide ring opening. Either a 1.2 halogen shift, with or without halogen elimination upon tautomerization, or 3-ol formation after arene ring cleavage would produce the ultimate products (Safe, et al. 1976; Safe, et al. unpublished, quoted in Sundstrom, et al. 1976a). The reactions are diagrammed in Figure 2. Other examples of PCBs for which metabolic pathways are consistent with arene oxide formation include 2, 2', 4, 4', 5, 5' -hexachlorobiphenyl in rabbits (Sundstrom, et al. 1976b) and 4 chlorobiphenyl and 4, 4'-dichlorobiphenyl in rats (Hass, et al. 1977). Infant Rhesus monkeys fed 2, 5, 2', 5 tetrachlorobiphenyl excreted dihydroxy, dihydrodihydroxy and dihydrotrihydroxy derivatives in urine (Hsu, et al. 1975b).

The K region epoxides of polyaromatic hydrocarbons are known to bind to nucleic acids in vitro (Grover and Sims, 1970) and in cultured mammalian cells (Grover, et al. 1975). Furthermore, they are capable of transforming cells in culture (Huberman, et al. 1972) although their significance in tumor induction in animals is in doubt (Grover, et al. 1975). It has been suggested that arene oxide metabolites of PCBs may react with nucleophilic sites in DNA and other macromolecules and that alkylation of critical sites may be involved in the induction of tumors (Allen and Norback 1977).


Cl
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OH
OH
Cl
Cl
% excreted in
faeces 0.7
urine 2.0
0.2
2.2
2.0
7.5

Figure 2: Metabolic pathways for 4, 4'-dichlorobiphenyl in the rabbit.

From: Sundstrom, et al. (1976a)

Excretion

The primary routes of PCB excretion are bile (observed in feces) and urine. Excretion is closely coupled to metabolism. In rats less than ten percent of excreted PCBs were unmetabolized (Matthews and Anderson, 1975b). The rate and efficiency of excretion were highly dependent upon the degree of chlorination and structure. Urinary excretion of PCBs accounted for the removal of 59.8, 33.9, 7.6, and 0.7 percent of total dose of mono, di, penta, and hexachlorobiphenyl respectively. Over 60 percent of urinary excretion occurred within the first 24 hours and all urinary excretion ceased by the ninth and fourth days, respectively, for penta- and hexachlorobiphenyl (Matthews and Anderson, 1975b). All the 2, 4, 5, 2',5' pentachlorobiphenyl excreted in urine by rats was in the form of a glucuronide conjugate of a metabolite (Chen and Matthews, 1974). While urinary excretion usually ceases within a few days, biliary excretion continues for an extended period. The relative contribution of biliary excretion to the elimination of PCBs increases with chlorination. The kinetics of excretion of mono- and dichlorobiphenyl are monophasic while the elimination of penta- and hexabiphenyl is biphasic. While 90 percent of PCBs up to pentachlorobiphenyl were excreted in 42 days or less, hexachlorobiphenyl was largely retained in the tissues of the animal. Extrapolation of the excretion data indicated that only 20 percent of 2, 4, 5, 2', 4', 5' hexachlorobiphenyl would even be excreted (Matthews and Anderson, 1975b).

The absence of adjacent unsubstituted carbons greatly decreased excretion as would be expected from the effects of structure on storage and metabolism. 3, 5, 3', 5' TCB is excreted at about the same rate as 2, 4, 5, 2', 5' pentabiphenyl (Tuey and Matthews, 1977; Matthews and Anderson, 1975a). While the half-life in fat for 2, 5, 2', 5' TCB was about 33 hours at 500 mg/kg dose in rats (Van Miller, et al. 1975) the half-life for 3, 5, 3', 5' TCB was 12 to 15 days at dose levels of .6 mg/kg in rats (Tuey and Matthews, 1977).

The half-lives of the individual PCB isomers in the rat may be approximated by the fecal half-lives which are 15.7 and 22.2 hours for mono and dichlorobiphenyl respectively. Penta and hexabiphenyls elimination is biphasic with first and second component half-lives of 39.2 and 211 hours for penta-CB and 49 and 642 hours for hexa-CB (Anderson, et al. 1977). Because only 20 percent of the hexa-CB is ultimately excreted its half-life is indefinite.

Rates of elimination of a series of tetrachlorobiphenyls in mice were determined by Mizutani, et al. (1977). Half-lives for TCB isomers in liver and the carcass ranged from 0.9 days for 2, 3, 2', 3' TCB to 9.2 and 7.8 days for the loss of 2, 4, 2', 4' from carcass and liver, respectively. Structure did not influence elimination as markedly as in the rat. 3, 5, 3', 5' TCB had half-lives of 2.1 and 2.2 days in carcass and liver. However, stimulation of metabolism by the addition of phenobarbitol did increase the rate of elimination of 2, 4, 2', 4' TCB more than 3, 5, 3', 5' TCB. The authors concluded that the rate-limiting step in the elimination of the isomers was release from storage in the tissues of the mouse rather than metabolism.

Two differences between the elimination of 2, 5, 2', 5' TCB in infant Rhesus monkeys and rats may be of interest in evaluating human metabolism. Single doses of 500 mg/kg to rats resulted in total elimination of about 76 percent (66 percent feces, 10 percent urine) in 72 hours (Van Miller, et al. 1975). In primates only one percent of the same dose was eliminated in feces and two percent in urine after 72 hours (Hsu, et al. 1975a). In addition, the major excreted metabolite in rats appeared to be 3-hydroxy TCB while a dihydrodiol TCB predominated in monkeys (Van Miller, et al. 1975; Hsu, et al. 1975b).

A final comment on the pharmacokinetics of PCBs must be addressed to transplacental and transmammary movement. Transplacental uptake of PCBs by a fetus has been documented in mice (Masuda, et al. 1978), rats (Curley, et al. 1973), Rhesus monkeys (Allen and Barsotti, 1976), and humans (Yoshimura, 1974). In mice, transplacental and transmammary uptake of PCBs were approximately 0.1 to 0.2 and 20 to 35 percent of total dose respectively (Masuda, et al. 1978). Similar values were observed in rats (Mizunoya, et al. 1974). Female monkeys consuming 2.5 ppm Aroclor 1254 transferred enough via breast milk to produce severe hyperplastic gastritis in nursing infants (Allen and Barsotti, 1976). Recently, a preliminary mathematical model of PCB distribution in rats has been proposed (Lutz, et al. 1977; Anderson, et al. 1977).

It should be noted that most of the laboratory studies discussed above have been performed with pure isomers, while toxicity studies and environmental exposures involve commercial mixtures with possible dibenzofuran contamination. In addition, commercial mixtures tend to contain asymmetrical polychlorinated biphenyls (Natl. Inst. Occup. Safety Health, 1977).

The pharmacokinetics of PCBs can be summarized with the following points:

1. They are readily absorbed through the gut, respiratory system, and skin.
2. They may initially concentrate in the liver, blood, and muscle mass; but long-term storage in mammals is primarily in adipose tissue and skin.
3. The major metabolic products of PCBs are phenolic derivatives or dihydrodiols which may be formed through pathways with arene oxide intermediates or by direct hydroxylation. The susceptibility of individual PCB isomers to metabolism is a function of the number of chlorines present on the biphenyl and their arrangement. Biphenyls which have one or more pairs of adjacent unsubstituted carbons are more rapidly metabolized than those which do not.
4. PCBs which are readily metabolized are also rapidly excreted in the urine and bile. Excretion in urine is most prominent for the least chlorinated, while bile becomes the more significant route of excretion for more highly chlorinated isomers.

5. Those isomers which are most refractory to metabolism accumulate for increasing periods of time in fatty tissues. Highly chlorinated isomers are accumulated almost indefinitely.

6. PCBs can be transferred either transplacentally or in breast milk.

7. Non-human primates may retain PCBs more efficiently than rodents.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Several reviews of the toxic effects of PCBs in animals and man have appeared in recent years (Kimbrough, 1974; Fishbein, 1974; Peakall, 1975; Kimbrough, et al. 1978; Cordle, et al. 1978; Natl. Inst. Occup. Safety Health, 1977 (which is particularly recommended for human effects)). This section will attempt to highlight the most significant toxic effects observed in animals and man, but will not seek to be comprehensive.

The acute oral and dermal LD_{50s} for PCBs in rats, mice, and rabbits are given in Tables 7, 8, and 9. In the classification by the American Hygiene Association the PCBs, are slightly toxic or almost nontoxic (Hodge and Sterner, 1949). In rats, Bruckner, et al. (1973) observed a 14-day LD_{50} of 4.25 g/kg. Toxic effects of high doses of Aroclor 1242 included diarrhea, chromoacryorrhea, loss of body weight, unusual stance and gait, lack of response to pain stimuli, and terminal ataxia. CNS deterioration and dehydrydration were thought to be contributing factors. Histopathologic changes were observed only in liver and kidney. Miller

TABLE 7

Acute Toxicity of PCB's in Several Strains of Rats and Mice.

Compound tested	Species and sex	Route	LD g/kg body weight	Reference[a]
Aroclor 1254	Rat (adult, Sherman strain)	Oral	4 - 10	(5)
Aroclor 1260	Rat (adult, Sherman strain)	Oral	4 - 10	(5)
Aroclor 1254	Rat (weanling, Sherman strain)	Oral	1.295	(5)
Aroclor 1260	Rat (weanling, Sherman strain)	Oral	1.315	(5)
Aroclor 1254	Rat (female, Sherman strain)	Intravenous	0.358	(5)
Aroclor 1221	Rat (female, Sherman strain)	Oral	4.00	(6)
Aroclor 1262	Rat (female, Sherman strain)	Oral	11.3	(6)
Aroclor 1240	Rat	Oral	4.25	(7)
Aroclor 1254	Rat (Wistar, 30-day-old, M-F)	Oral	1.3	(8)
Aroclor 1254	Rat (Wistar, 60-day-old, M-F)	Oral	1.4	(8)
Aroclor 1254	Rat (Wistar, 120-day-old, M-F)	Oral	2.0	(8)
Aroclor 1254	Rat (Wistar, 120-day-old, F)	Oral	2.5	(8)
Kaneclor-400	Rat (Wistar, M)	Oral	1.30 (ml kg)	(9)
Kaneclor-400	Rat (Wistar strain, F)	Oral	1.14 (ml kg)	(9)
Kaneclor-400	Mice (CFI strain, M)	Oral	1.875 (ml kg)	(9)
Kaneclor-400	Mice (CFI strain, F)	Oral	1.57 (ml kg)	(9)
Kaneclor-300	Rat (Wistar strain, M)	Oral	1.15	(9)
Kaneclor-300	Rat (Wistar strain, F)	Oral	1.05	(9)
BP-200 biphenyls of dichloride and below	Mice (dd strain, F)	Oral	6.36	(10)
2,4'-Dichlorobiphenyl	Mice (dd strain, F)	Oral	7.86	(10)
Trichlorobiphenyl	Mice (dd strain, F)	Oral	3.06 - 4.25	(10)
Biphenyl of trichloride and below	Mice (dd strain, F)	Oral	9.27	(10)
2,4,3',4'-Tetrachlorobiphenyl	Mice (DVI strain)	Intraperitoneal	2.15	(11)
5-OH derivative of 2,4,3',4'-tetrachlorobiphenyl	Mice (CFI strain)	Intraperitoneal	0.43	(11)
[illegible],3',4'-Pentachlorobiphenyl	Mice (CFI strain)	Intraperitoneal	0.65	(11)

[a] Reference number [illegible] from source.

[illegible] Kimbrough, [illegible] 1978.

TABLE 8

Oral LD_{50} (rat)[a]

Compound tested		LD g/kg body weight
Aroclor 1221	(Undiluted)	2.000 - 3.169
Aroclor 1232	(Undiluted)	1.26 - 2.0
Aroclor 1242	(Undiluted)	0.794 - 1.269
Aroclor 1248	(Undiluted)	0.794 - 1.269
Aroclor 1260	(50% soln in corn oil)	1.26 - 2.0
Aroclor 1262	(50% soln in corn oil)	1.26 - 3.16
Aroclor 1268	(33.3% soln in corn oil)	2.5

[a] Data of Panel on Hazardous Substances (6).

From: Kimbrough, et al. (1978)

TABLE 9

Skin LD_{50} (rabbits)[a]

Compound tested		LD g/kg body weight
Aroclor 1221	(Undiluted)	3.98
Aroclor 1232	(Undiluted)	4.47
Aroclor 1242	(Undiluted)	8.65
Aroclor 1248	(Undiluted)	11.0
Aroclor 1260	(50% soln in corn oil)	10.0
Aroclor 1262	(50% soln in corn oil)	11.3
Aroclor 1268	(50% soln in corn oil)	10.9

[a] Data of Panel on Hazardous Substances (6).

From: Kimbrough, et al. (1978)

(1944) found the guinea pig most sensitive to Aroclor 1242 followed by the rabbit and rat. In the rat, toxicity decreased with increasing degree of chlorination; however, the effect was not observed with rabbits (Fishbein, 1972).

The more significant toxic effects of PCBs are observed on repeated exposure over a period of time. Aroclor 1254 at 1000 ppm in the diet was fatal to 75 percent of male rats in 43 days with total intakes of 500 to 2000 mg/kg being lethal (Tucker and Crabtree, 1970). Phenoclor DP6 fed at 2000 ppm to rats resulted in marked weight loss and death between 12 and 56 days after the initiation of treatment (Vos and Koeman, 1970). Guinea pigs treated dermally for 11 days with a total of 379.5 mg of a PCB with 42 percent average chlorine content died at intervals up to 21 days following the first application (Miller, 1944). Aroclor 1254 at 1000 ppm in the diet killed 5/10 male rats and 8/10 female rats. At 500 ppm over eight months two males and one female died while no lethality was observed at 100 or 20 ppm. Aroclor 1260 was less toxic, with 8/10 females but no males dying at 1000 ppm. No males died at lower doses and 1/10 and 2/10 females died at 100 and 500 ppm respectively. Substantial weight losses were observed at 100 and 500 ppm in both males and females (Kimbrough, et al. 1972). Mink have been shown to be unusually sensitive to PCBs. A mixture of Aroclors 1242, 1248 and 1254 at 30 ppm in the diet for 6 months was 100 percent lethal (Aulerich, et al. 1973) as was 3.6 ppm Aroclor 1254 over 105 days in another study (Plantonow and Karstad, 1973). Adult Rhesus monkeys (Macaca mulatta) were particularly sensitive to

PCBs. Aroclor 1248 at 100 or 300 ppm in the diet for two to three months resulted in extreme morbidity within one month and almost 100 percent mortality within three months. Total intakes for the two groups were 0.8 to 1.0 g for 100 ppm and 3.6 to 5.4 g for 300 ppm (Allen, 1975).

The most consistent pathological changes occurring in mammals after PCB exposure are in the liver. In rats, rabbits, and guinea pigs, Miller (1944) observed fatty deposits after acute injections and similar changes in rabbits and guinea pigs after dermal application. In feeding experiments, marked fatty metamorphosis was noted in guinea pig liver with intracellular hyaline bodies being observed in rats. Less striking changes were noted in the kidneys, lungs, adrenals, and heart of guinea pigs. Rats exposed repeatedly to dietary PCBs show increased liver weights (Kimbrough, et al. 1972; Bruckner, et al. 1973). Kimbrough, et al. (1972) fed rats Aroclor 1254 or 1260 at levels between 20 and 1000 ppm for eight months. Light microscopic changes observed included hypertrophy of liver cells, cytoplasmic inclusions, brown pigment in Kupffer cells, lipid accumulation and, at higher doses, adenofibrosis. Ultrastructural examination revealed an increase in smooth endoplasmic reticulum. The effect of Aroclor 1254 was more pronounced than that of 1260. Porphyria was observed in the livers and, occasionally, other tissues of animals exposed to either mixture.

Rats fed 2000 ppm Phenoclor DP6 also had enlarged livers with vacuolated foamy cells containing pycnotic nuclei (Vos and Koeman, 1970). Vacuolization of liver cells was also noted by Bruckner, et al. (1973) after dosing rats with 100 mg/kg Aroclor for three weeks although no overt toxicity was manifest.

Rats fed 100 ppm Aroclor 1242 (6.6 to 3.89 mg/kg/day) or Aroclor 1016 (6.9 to 3.5 mg/kg/day) for periods of up to ten months showed no signs of overt intoxication or gross liver changes. Enlarged hepatocytes with vacuolated cytoplasms and inclusions were noted. Aroclor 1242 seemed to produce more pronounced changes than 1016. Four and six months after the discontinuation of exposure hepatocytes were still enlarged but cytoplasmic vacuoles and inclusions had diminished, suggesting a degree of reversibility of effect. Significant residual levels of PCBs remained in adipose tissue. Using electron microscopy, increased smooth endoplasmic reticulum and lipid vacuoles as well as atypical mitochondria were observed. No significant gross changes in other organs were noted (Burse, et al. 1974).

Allen and Abrahamson (1973) fed rats 1000 ppm of either Aroclor 1248, 1254, or 1262 for 1, 3, 7, 14, 21, or 28 days or 6 weeks. No overt toxicity was observed although weight gain was retarded in all treated groups. The effect was inversely proportional to percent chlorination. Increased liver size, protein, and RNA content were observed. The magnitude of changes increased with the percent chlorination. Hypertrophy was associated with proliferation of the smooth endoplasmic reticulum, formation of membranous arrays, and increased lipid droplets.

The effect of metabolism on toxicity was explored by giving rats large (1.5 g/kg) single doses of 2, 5, 2', 5'-tetrachlorobiphenyls which produced high mortality within two to three days (Allen, et al. 1975). Pretreatment with phenobarbitol to induce metabolic enzymes allowed survival without obvious ill effects following a 1.25 g/kg dose, while treatment with the microsomal enzyme inhibitor SKF 525A lead to 100 percent mortality in four days. The ability to metabolize and eliminate TCB appears to protect the animal. Dietary administration of 100 ppm TCB for three weeks produced less liver hypertrophy than Aroclor 1248.

Liver pathology in mice exposed to 1.5 mg PCB/day was essentailly the same as seen in rats, including increased smooth endoplasmic reticulum and increased lipid droplets (Nishizumi, 1970).

Rabbits receiving 300 mg orally of Aroclor 1221, 1242, or 1254 for 14 weeks were examined (Koller and Zinkl, 1973). Aroclor 1221 and 1242 treated rabbits gained weight at control rates while 1254 treated rabbits did not gain as much. Livers of 1254 and 1242 treated animals were enlarged while livers of 1221 treated animals were smaller than controls. Gross liver lesions and small uteri were apparent in the 1254 treated animals but not the others. Liver pathology in 1254 treated animals included enlarged hepatocytes with foamy to granular cytoplasms, and subcapsular midzonal necrosis. Aroclor 1242 produced a liver pathology similar to 1254. Aroclor 1221 treated animals were free of histologic changes.

Dermal studies with rabbits using Clophen A60, Phenoclor DP6 and Aroclor 1260 indicated that the latter was the least toxic (Vos and Beems, 1971). The former two mixtures had been shown to be contaminated with tetra- and penta-chlorodibenzofuran (Vos, et al. 1970). Skin lesions produced included hyperplasia and hyperkeratosis of the epidermal and follicular epithelium, and were accompanied by pathological changes in the liver and kidney. The chlorodibenzofuran impurities in the PCBs were thought to be responsible for the skin lesions. A comparison of the toxic effects of dermally applied 2, 4, 5, 2', 5' hexachlorobiphenyl and Aroclor 1260 demonstrated that the skin lesions appeared sooner and were more severe after treatment with the commercial mixture. Liver changes were found in both treatment groups with the pure isomer inducing the more severe effects. From this study it was concluded that the chlorodibenzofuran contaminants in commercial mixtures probably contribute to the skin lesions (chloracne), edema formation, and liver damage while PCBs contribute in lesser degrees to chloracne and liver damage but are primarily responsible for the hepatic porphyria observed in PCB intoxication (Vos and Notenboom-Ram, 1972).

Non-human primates are rather sensitive to PCBs. Male Rhesus monkeys were fed 300 ppm Aroclor 1248 for three months. Effects which began to appear within a month included hair loss, subcutaneous edema, purulent discharge from the eyes, acneform eruptions, and liver hypertrophy caused by smooth endoplasmic reticulum proliferation. Marked hypertrophy of the gastric mucosa was a significant finding not usually seen in rodents. Invasion of the submucosa by the mucosal epithelium with increased cellularity and dysplasia occurred in the stomach. The dietary levels used were about tenfold greater than the contamination levels in foods during the early 1970's and the gastric changes observed were considered to be of particular significance to human risk (Allen and Norback, 1973). When fed low levels (2.5 and 5 ppm) of Aroclor 1248 for 52 weeks female monkeys developed periorbital edema, alopecia, erythema and acneform lesions. Effects in males were less pronounced (Barsotti and Allen, 1975). The high sensitivity of monkeys to PCBs has been confirmed and the evaluation of the toxic effects, particularly in the gastric mucosa, has been extended (McNulty, 1976; Bell, 1976). The pathologic effects of PCBs in nonhuman primates have been reviewed by Allen and Norback (1976) and Allen (1975).

The ability of PCBs to induce liver microsomal enzymes was demonstrated by Street, et al. (1969). Enzyme induction by commercial PCBs has been shown in rabbits (Villeneuve, et al. 1971a), rats (Litterst and VanLoon, 1972), and primates (Allen, et al. 1974). In rats induction is observed following intraperitoneal injection (Bickers, et al. 1972) or skin application (Bickers, et al. 1975). Threshold values for enzyme induction vary between 0.5 and 25 ppm (Villenueve, et al. 1971a; Litterst, et al. 1972; Turner and Green, 1974). The induction of demethylating activity in rats by Aroclor 1254 was maximum in seven days while cytochrome P450 and nitroreductase activities continued to rise over four weeks of treatment. Activities declined slowly after discontinuation of treatment reaching control levels in about ten days (Litterst and VanLoon, 1974). Cutaneous exposure to PCBs resulted in a maximum induction within two to six days. (Bickers, et al. 1972, 1975). Degree of induction of enzyme activities was found to correspond to increasing chlorine content of Aroclors (Litterst, et al. 1972) and of di. tetra, and hexachlorobiphenyl mixtures (Schmoldt, et al. 1974). The effects of chlorine content and position of pure isomers were examined by Johnstone, et al. (1974), Ecobichon (1975), and Ecobichon and Comeau (1975). More highly chlorinated isomers and those substituted at the 4 and 4' positions were most active in inducing enzymes associated with the endoplasmic reticulum. For less localized enzymes, position was less critical, although chlorinated compounds were more effective than biphenyl.

The effects of dietary exposure to Aroclor 1254 on enzyme induction were investigated in rats by Bruckner, et al. (1977). Aroclor 1254 at 5 or 25 ppm induced dose dependent increases in the metabolism of pentobarbitol, aminopyrine, and acetanilide after 35, 70, and 140 days of exposure. Exposure to 1 ppm had little effect on metabolism. Liver weight and serum triglyceride levels were elevated only in animals exposed to 25 ppm. In 15-day experiments induction of aminopyrine N-demethylation was observed after the first day of exposure at 5 and 25 ppm, and acetanilide hydroxylation was induced after two days. Aminopyrine N-demethylation returned to normal 15 days after the termination of exposure. Consumption of as little as 1 to 2 mg of PCBs in 24 hours was sufficient to stimulate acetanilide hydroxylation.

Commercial PCBs have been shown to induce cytochrome P450 (phenobarbitol type) and cytochrome P448 (3 methylcholanthrene type) (Alvares, et al. 1973). More recent studies with purified isomers indicated that ortho-para-substituted PCBs induce P450 while meta-para-substituted PCBs induce P448. Substitution in the ortho-position dominates over meta and no isomers were found to induce both activities (Goldstein, et al. 1977). The induction of both systems by commercial preparations and some purified isomers has recently been shown to result from contamination with dibenzofurans. Even "99 percent pure" isomeric PCBs containing 44 ppm tetrachlorodibenzofuran effectively induces P448 while more rigorously purified material does not (Goldstein, et al. 1978). This observation serves as a reminder that the effects of trace contaminants must be kept in mind when evaluating the toxic effects of PCBs.

Enzyme inducing effects of PCBs have also been examined in vivo by the observation of shortened phenobarbitol sleeping times in PCB treated animals (Bickers,et al. 1972; Johnstone, et al. 1974; and Villeneuve, et al. 1972). PCB induction of enzyme activities in other tissues has included skin (Bickers, et al. 1975) placenta and fetus (Alvares and Kappas, 1975), neonatal liver during lactation (Alvares and Kappas, 1975), and lung and kidney (Vainio, 1974).

Other systemic effects of PCBs in mammals include porphyria (Bruckner, et al. 1974), increased thyroxin metabolism (Bastomsky, 1974) and ultrastructural changes in the thyroid (Collins, et al. 1977), inhibition of ATPases (LaRocca and

Carlson, 1975), and interference with oxidative phosphorylation (Sivalingan, et al. 1973). Alterations in steroid hormone metabolism are produced by PCBs in rats (Bitman and Cecil, 1970), mice (Orberg and Kihlstrom, 1973), and other animals. Aroclor 1254 appears to reduce liver vitamin A concentrations in pregnant rabbits (Villeneuve, et al. 1971b). A more complete review of these effects can be found in Matthews, et al. (1978).

PCBs have been shown to have immunosuppressive effects in rabbits (Vos and Beems, 1971; Street and Sharma, 1975), guinea pigs (Vos and van Genderen, 1973; Vos and DeRoij, 1972), monkeys, mice (Thomas and Hinsdill, 1978), and several birds. Significant effects were observed in Rhesus monkeys exposed to dietary levels of Aroclor 1248 as low as 5.0 ppm.

Effects of Aroclor 1254 and 1260 on reproduction in Sherman strain rats were investigated (Linder, et al. 1974). Dietary levels of 5 ppm Aroclor 1254 had no effect on reproduction in rats exposed through two generations. Liver weights were increased in male and female offspring of the F_1 and F_2 generations. At 1 ppm, Aroclor 1254 caused increased liver weights in F_1 male weanlings. At 20 ppm Aroclor 1254 the number of pups in the F_{1b} and F_2 generations was reduced while 100 ppm resulted in increased mortality in F_{1b} offspring and decreased the mating performance of F_{1b} adults. Aroclor 1260 produced increased liver weights in F_1 offspring at 5 ppm but did not affect reproduction at 100 ppm. At 500 ppm litter sizes were reduced and survival was decreased in F_1 litters. Pregnant rats given 100 mg/kg/day Aroclor 1254 on days 7 to 15 had grossly normal litters but only 30.1 percent survived to weaning. Dosage rates of 50 mg/kg/day Aroclor 1254 or 100 mg/kg/day Aroclor 1260 did not affect reproduction or pup survival.

Rabbits fed 0.1 or 1.0 mg/kg body weight Aroclors 1221 or 1254 showed no significant decrease in number of pregnancies or number of fetuses per litter (Villeneuve, et al. 1971a). No induction of fetal liver enzymes could be detected. However, administration during gestation of 600-2, 500 ppm Aroclor 1254 in the diet resulted in resorptions, abortions, maternal death and, in two fetuses, asymmetric skulls (Villeneuve, et al. 1971b).

Reproductive effects in mice were investigated in animals treated for ten weeks with 0.025 mg/day Clophen A60 (Orberg and Kihlstrom, 1973). The length of the estrus cycle was increased from 6.6 days in controls to 8.7 days in experimental animals. Also the percentage of implanted ova was reduced from 87.0 to 79.5. In a second study the reproductive effects of neonatal exposure to PCBs in milk were examined by injecting lactating female mice with Clophen A60. On the day of parturition and at weekly intervals for three weeks, the females were injected with 50 mg of PCB. When treated male and female offspring were mated with each other, the percent implantation dropped from a control level of 94 percent to 75 percent (Kihlstrom, et al. 1975).

In female Rhesus monkeys exposure to 25 ppm Aroclor 1248 in the diet for two months lead to the typical effects of PCB intoxication for monkeys including edema, alopecia, and acne. One animal ingesting a total of 450 mg PCB died two months after exposure ended and was found to have hyperplastic gastritis and bone marrow hypoplasia. The remaining five animals were bred three months after treatment. Three were thought to have conceived but resorbed or aborted the embryos in the first two months of pregnancy. One delivered a fully developed but small infant (Allen, et al. 1974).

In a more fully developed study both male and female Rhesus monkeys were fed either 2.5 or 5.0 ppm Aroclor 1248 in the diet (Barsotti and Allen, 1975; Barsotti, et al. 1976). The total intake in the first 6 months for the females was 180 and 364 mg for the 2.5 and 5.0 ppm diets, respectively. Untreated females bred to treated males had normal rates of conception (Barsotti and Allen, 1975). Treated females bred to normal males produced the following rates of conception: control, 12/12; 2.5 ppm, 8/8; 5.0 ppm, 6/8. Live births resulting from the conceptions were: control, 12/12; 2.5 ppm, 5/8; 5.0 ppm, 1/6. In the 2.5 ppm group, three fetuses were resorbed shortly after conception. In 5.0 ppm group three pregnancies aborted at 46, 67, and 107 days of gestation, one fetus was resorbed, one was stillborn, and one normal birth occurred. The two females who failed to conceive were subsequently bred five times without conception. The live born infants were of low birth weight and showed signs of PCB intoxication after nursing their mothers for less than two months. Three infants died 44 to 112 days after birth (Barsotti, et al. 1976). The mothers' breast milk contained 0.154 to 0.397 ppm PCBs and one contained 16.44 ppm (fat basis) (Allen and Barsotti, 1976). It should be noted that the dose levels producing these rather striking effects are within the range of contamination of the human diet observed until the mid 1970's.

Recently, adipose tissue levels of PCBs in infant Rhesus monkeys exposed *in utero* and via breast milk have been correlated with behavioral effects (Bowman, et al. 1978). Three of five infants born to mothers exposed to 2.5 ppm Aroclor 1248 in the diet during pregnancy and lactation survived over four months. PCB levels in fat tissue in the infants declined with a first order rate constant over a period of 8 to 23 months of age. Extrapolated maximum PCB levels were 21, 114, and 123 ug/g fat. A battery of eleven behavioral tests was conducted with the three exposed animals and four controls over this time period and a positive correlation between reduced performance and PCB body burden was observed for seven tests.

Mink have been found to be exceedingly sensitive to PCB-induced reproductive failure. A marked increase in kit mortality was observed in commercial mink in the mid-1960's after fish meal derived from spawning Great Lakes Coho salmon was incorporated into the diet. Laboratory studies confirmed that the reproductive losses were related to the ingestion of Great Lakes fish (Aulerich, et al. 1971) and subsequent investigation showed that PCBs contaminating the fish meal were the probable toxic agents (Ringer, et al. 1972). When fed 10 ppm each of Aroclors 1242, 1248, and 1254 (30 ppm total) 11/11 adult female mink died prior to the end of the normal whelping (delivery) period (Ringer, et al. 1972). Aroclor 1254 fed at 10 ppm resulted in no offspring among six females. At 5 ppm, Aroclor 1254 fed for four months prior to whelping depressed reproduction with only 3 of 12 females whelping and 3 of 9 kits born alive. At 1 ppm Aroclor 1254, 8 of 10 females whelped and 35 of 43 kits were born alive. Among control animals 11 of 11 whelped and 56 of 66 pups were alive at birth. The reproductive toxicity of Aroclor 1254 becomes pronounced between 1 and 5 ppm in the diet (Ringer, et al. 1972). At 2 ppm in a nine month feeding trial, Aroclor 1254 significantly reduced reproduction while Aroclors 1016, 1221, and 1242 did not (Aulerich and Ringer, 1977). Assuming a food intake of 150 gm/day (Schaible, 1970) the total PCB intake in the two trials would have been 90 mg at 5 ppm for four months or 61 mg at 2 ppm for nine months (Aulerich and Ringer, 1977).

Human exposures to PCBs resulting in toxic effects have almost all resulted from the ingestion of rice oil contaminated with Kanechlor 400 in Japan or from industrial exposure. While absorption through the gut was the route of exposure in the former case, occupational exposures occur largely by inhalation or absorption through the skin.

Yusho, the disease resulting from the ingestion of contaminated rice oil in Japan, has been the subject of continuing study since the episode of exposure in 1968.

Periodically, special reports on these continuing studies have been published in Fukuoka Acta Med (Vol. 60, 1969; Vol. 62, 1971; Vol. 63, 1972; Vol. 65, 1974; Vol 66, 1975; Vol. 68, 1977). These results, largely published in Japanese, have been reviewed in English by the Japanese investigators both early in the study (Kuratsune, et al. 1972; Kuratsune, 1972) and more recently (Kuratsune, et al. 1976). The cause and scope of the exposure of the Japanese public has been described above (See Ingestion from Food). The initial symptoms of Yusho included increased eye discharge and swelling of upper eyelids, acne-form eruptions and follicular accentuation, and pigmentation of the skin. Other symptoms including dermatologic problems, swelling, jaundice, numbness of limbs, spasms, hearing and vision problems, and gastrointestinal disturbances were prominent among the complaints of patients seen within the first eight months after exposure (Kuratsune, et al. 1972). The first patients were seen almost immediately after the release of the contaminated oil in February 1968. Of a group of patients seen between October 1968 and January 1969, 55 percent became ill between June and August. It was ultimately determined that as many as 63.9 percent of those who consumed contaminated oil became ill. Among a group of 146 known users of the oil, 80 consumed less than 720 ml and 88 percent of these users were affected. Among those who used more than 720 ml, 100 percent were affected. The clinical severity of symptoms did not differ by sex but the age group 13 to 29 was more affected than others (Kuratsune, et al. 1972).

The analysis of the oil indicated that it contained between 2 and 3 mg/kg of Kanechlor 400 (Kuratsune, et al. 1972). It was later discovered that Kanechlor 400 contained 18 ppm of polychlorinated dibenzofurans (PCDFs) and that the PCDF concentration in "Yusho Oil" was about 5 ppm (Nagayama, et al. 1975). The PCDF level in the oil was 250 times greater than would be expected based on the level in fresh Kanechlor 400, leading Kuratsune, et al. (1976) to suggest that the concentration increased with PCB use as a heat transfer medium.

The amounts of Kanechlor 400 ingested were estimated for the original 146 person study group. The average amount ingested was estimated to be 2 g while the minimum amount ingested by a patient was about 0.5 g (Kuratsune, et al. 1972).

Laboratory evaluations of patients during the early period were summarized by Kuratsune (1972). Several changes in blood were noted, including decrease in erythrocyte count, increase in leukocyte count, and increase in serum lipids, particularly triglycerides. Blood proteins, electrolytes, and enzyme activities were normal in most instances. Some increases in urinary ketosteroid excretion were observed. The "cheesy" material from Yusho acne contained more steric and oleic acids than did "normal acne", but less myristic palmitic and palmitoleic acid. Linoleic acid was present in Yusho acne but not "normal acne." Liver biopsy indicated hypertrophy of the smooth endoplasmic reticulum, reduction of the rough endoplasmic reticulum, filamentous inclusions, and mitochondrial abnormalities. Skin changes included hyperkeratosis, cystic dilatation of the hair follicles and marked increase of melanine in basal cells of the epidermis. Decreased sensory nerve conduction velocities were observed in 9 of 23 patients. Abnormalities of the eyes included hypersecretion of the meibomian gland, and abnormal pigmentation of the conjunctiva.

Thirteen women, 11 with Yusho and 2 without, but married to men with Yusho, delivered ten live and two stillborn infants between February 15 and December 31, 1968. Nine of the ten had grayish-dark stained skin, and five had similar pigmentation of the gingiva and nails. Eye discharge was common. A stillborn fetus had marked hyperkeratosis, atrophy of the epidermis, and cystic dilatation of the hair follicle. Increased melanin pigment in the blood cells and the epidermis was also noted. Twelve of the 13 fetuses were small for date of birth. The growth of children affected by Yusho was significantly lower than Japanese national standards. A detailed clinical study of four Yusho babies showed that they were small for their age, had dark pigmentation on skin and mucous membranes, and gingival hyperplasia. Teeth were erupted at birth, spotted calcification of the parietooccipital skull, wide fontanels, and saggital suture was present, along with facial edema and exophthalmic eyes (Yamashita, 1977).

By three years after the episode about half the patients were improving while 40 percent were essentially unchanged and 10 percent were becoming more severely affected. Even among those said to be improving, many still complained of persistant headaches, general fatigue, weakness and numbness of limbs, weight loss, and other problems (Kuratsune, et al. 1972).

An evaluation of the longer-term effects of Yusho has been summarized by Kuratsune, et al. (1976). In 1972 Masuda noted a peculiar gas chromatographic pattern of PCB fractions which was common to blood, tissues and breast milk of Yusho patients (Koda and Masuda, 1975). A pattern seen in about 60 percent of Yusho patients contained a larger amount of a late eluting peak than PCB-containing tissues resulting from other types of exposures. This pattern was referred to as type A. A similar pattern seen in about 37 percent of Yusho patients was referred to as type B. These two patterns (types A and B) have never been observed in individuals (human or animal) exposed to PCBs in other situations. These types appear unique to Yusho. Tissue levels of PCBs in patients undergoing surgery or who died and were autopsied were followed over several years. Adipose tissue levels were high (13 to 76 ppm) shortly after the end of exposure but were substantially lower by the next year. By 1970 and beyond, tissue levels were within the normal range in the cases studied. Blood levels were not determined until 1972 by which time they were in the normal range. Patients whose plasma PCB pattern was type A had higher levels than those with type B.

The discovery of substantial levels of PCDF in Yusho oil has been discussed. Levels of PCDFs in control individuals and Yusho patients were determined. No detectable (0.1 ppb) PCDFs were found in controls while tissues of patients who died in 1969 and 1972 contained .009 and .013 ppm in adipose and liver respectively. Ratios of PCB/PCDF were 144 and 4 for adipose tissue and liver, respectively. PCDF levels were higher in liver than adipose on a fat basis. Although the sample was small, the levels in whole adipose tissue appeared to have dropped to about 1/3 of the 1969 level by 1972.

By 1972 the dermal and mucosal signs which were most marked in the initial stages of toxicity were gradually improving. Symptoms considered to be due to internal disturbances, such as fatigue, poor appetite, abdominal pain, headache, pain and numbness in the limbs, and cough and expectoration of sputum, have become more prominent. Between March 1973 and April 1974, 79 patients were examined and blood PCBs evaluated (Koda and Masuda, 1975). Of patients with type A or B plasma PCB chromatographic patterns a majority exhibited some or all of the typical spectrum of dermatological symptoms with frequencies in type A patients being higher than in type B patients. Because PCB levels in type A patients were higher than in type B, the severity of symptoms was correlated with blood PCB levels.

Serum triglyceride levels in males did not decline significantly between 1969 and 1974 (Okumura, et al. 1974). Levels in female patients declined but were still above normal. The elevation of triglycerides correlated with increased blood PCB levels and the type A pattern.

Serum bilirubin in patients was lower in 121 patients than in 257 controls, indicating an accelerated rate of disposal (Hirayama, et al. 1974).

Long-term effects continued to be observed in children born to Yusho mothers. Nine infants with dark brown skin pigmentation were born to Yusho mothers between 1969 and 1972, three of them to a patient between 1969 and 1971 (Yoshimura, 1974). The plasma PCB levels of 30 children born to 18 Yusho mothers were significantly above control levels but lower than maternal levels (Abe, et al. 1975). Children nursed by their mothers had higher levels than children who were not breast fed. One case was reported by Yoshimura (1974) in which a baby was thought to have acquired Yusho solely as a result of breast milk intake.

Masuda, et al. (1974) found PCB levels in breast milk of five Yusho women between 0.03 and 0.06 ppm which was just within the normal range. A recent study of PCB levels in the breast milk in 400 Japanese women detected average levels of 0.033, 0.026, and 0.029 ppm in three measurements made at two month intervals (Yakushiji, et al. 1977). Based on these levels, they calculated that daily intake by a nursing infant would be 24 µg/day. This can be compared to an average dietary intake by Japanese adults of 21 µg/day or 9 µg/day by U.S. adults. By April 30, 1975, 29 of 1,291 Yusho patients had died. Among 22 who died before September, 1973, 9 deaths resulted from malignant neoplasms (Urabe, 1974).

The occurrence of Yusho symptoms after modest PCB intake coupled with the similarity of many of the symptoms to those seen in animals, particularly primates, suggests that the toxic effects observed in animals must be considered potentially accurate models for humans. The persistence of symptoms in Yusho patients is a particular source of concern. The major uncertainty regarding toxicity in Yusho patients rests with the unknown effects of the PCDFs present in unusually high concentrations in Yusho oils.

Early reports of toxic effects of occupational PCB exposure are not easily interpreted because a mixture of compounds including chloronaphthalenes was present. A fatal case resulted from exposure to a mixture of 90 percent chloronaphthalenes and 10 percent PCBs (Drinker, et al. 1937). The subject developed chloracne, followed by jaundice and abdominal pain, and was found to have cirrhosis of the liver at autopsy.

Many studies of occupational exposure have shown varying degrees of toxicity under different conditions. The following discussion will highlight studies which indicate the types of toxic reactions commonly observed in occupational exposures and the levels of sensitivity in different situations. A detailed review of occupational exposure to PCBs has recently been prepared (Natl. Inst. Occup. Safety Health, 1977).

Elkins (1959) found that average PCB concentrations in the workroom air of several plants in Massachusetts ranged from 0.1 to 5.8 mg/m^3 while peak concentrations were between 0.2 and 10.5 mg/m^3. No immediate toxic effects were seen;

however, exposure to 10 mg/m^3 was said to be unbearably irritating. Three cases of severe chloracne were reported in a work environment in which PCB air levels were found to be between 5.2 and 6.8 mg/m^3. The workers developing chloracne had been exposed for 2 to 4 years. No alterations in liver function or other abnormalities were found (Puccinelli, 1954).

An analysis of the health effects of PCBs on eight laboratory workers involved in testing dielectric fluids was made by Levy, et al. (1977). The workers, all males 25 to 49 years of age, had been employed 2.5 to 18 years. Breathing zone, point source, and general work area samples were collected on three occasions. The ranges observed were: breathing zone, 0.014 to 0.073 mg/m^3; point source (near an oven), 0.042 to 0.264 mg/m^3; and room area, 0.013 to 0.15 mg/m^3. Blood PCB concentrations were 36 to 286 ppb which is substantially above the range in several studies of general populations (Finklea, et al. 1972). Workers complained of dry sore throat (6/8), skin rash (3/8), gastrointestinal disturbances (3/8), eye irritation and headache (2/8). Examination disclosed one patient with skin rash, two with nasal irritation, one showing rales, and four with high blood pressure, but no abnormalities in liver function.

Toxic effects from a low level exposure were reported by Meigs, et al. (1954). A leaking heat exchanger in a chemical plant discharged PCB vapors. No employees worked routinely at the point of leakage but breathing zone levels in work areas were found to be 0.1 mg/m^3. The period of exposure was 19 months. Seven of 14 exposed workers developed mild to moderate chloracne after exposure durations of 5 to 14 months. Liver function tests showed normal serum bilirubins, 24- and 48-hour cephalin flocculations, thymol turbidities and serum alkaline phosphatase activities in six of the seven workers, but borderline increases in cephalin flocculation and thymol turbidity in the seventh. After thirteen months, the thymol turbidity but not the cephalin flocculation had improved.

A study of PCB exposure in six Japanese industrial plants has been reported (Hasagawa, et al. 1972; Hara, et al. 1974, 1975). Although the original publications are in Japanese, a detailed description in English is available (Natl. Inst. Occup. Safety Health, 1977). PCBs were manufactured in one plant, used in manufacturing capacitors in four plants, and had been used in a fifth plant until one month before the study began. The sixth plant used biphenyls, not PCBs. PCB concentrations in air as both vapor and particulates were determined. The lowest levels in one plant were 13 to 15 $\mu g/m^3$ vapor and 4 $\mu g/m^3$ particulate while the highest levels in a single plant were 95 to 965 $\mu g/m^3$ vapor, 73 to 650 $\mu g/m^3$ particulate. Except in the instance of a spill, vapor concentrations always exceeded particulate concentrations. Blood PCB levels in 99 workers were found to average 370 ppb as compared to values in 20 controls averaging 20 ppb. No correlation between duration of exposure and blood level could be found in data from three of the plants. Dermal effects found were chromodermatosis of the dorsal joints of the hands and fingers and of the nail bed, and acneform exanthema. Dermal effects seemed unrelated to blood levels, suggesting that they resulted directly from skin contact. Changes in fat metabolism and mild disturbances in liver function were found. The consequences of termination of PCB exposure were examined by following 38 current and 80 former workers from 1972 to 1975 who were from the plant which had discontinued PCB use. During the period of PCB exposure, 17 capacitor immersion process workers had blood levels of 7 to 300 ppb, which were closely related to years of exposure. One year after cessation of exposure, blood PCB levels decreased but not uniformly. The average decrease was about 75 percent of the original value. The blood half-lives of PCBs were determined and found to be related to the number of years of exposure. For 1 year of exposure, $T\frac{1}{2}$ = 3 months, while for 10 to 15 years exposure, $T\frac{1}{2}$ = 30 months. The investigators concluded that blood served only as a PCB carrier while fat served as the depot tissue. Many of the employees complained of blackheads, acne, and skin irritation while working with PCBs; however, these conditions cleared markedly after exposure ceased. Serum triglyceride levels in workers were elevated in correlation with blood PCB levels.

A study in Australia by Ouw, et al. (1976) examined two groups of workers with different levels of exposure in a capacitor manufacturing facility. One group (inside) worked in an impregnation process where exposure to heated (70^{o}C) Aroclor 1242 occured. The second group (outside) assembled cool Aroclor-dipped components in a location separate from the first group. The entire group had an average blood

PCB level near 400 ppb. The distribution of individual Aroclor components differed between the groups with the outside workers being low in early eluting (on gas chromatography) fractions but elevated in late eluting fractions relative to the inside group. No abnormalities in liver function were observed but skin irritation and eczematous rashes were observed. One worker had chloracne but no systemic effects. The severity of dermal effects was not clearly correlated to blood PCB level. Breathing zone air concentrations in the impregnation room varied from 2.22 to 0.32 mg/m^3. To bring conditions within government guidelines, improved exhaust ventilation was installed and workers were encouraged to wear impervious gloves to reduce skin absorption. These actions reduced atmospheric PCB levels to 0.75 to 0.08 mg/m^3. After two months, new blood samples were taken which indicated that a slight increase in blood levels had occurred. Failure to wear gloves was the reason cited for the failure to improve blood levels.

A recent study of liver function in Aroclor 1016-exposed workers illuminates the sensitivity of the liver to exposure (Alvares, et al. 1977). Antipyrene clearance was determined in five workers who had been occupationally exposed to PCBs for at least four years and Aroclor 1016 for at least two years. None of the workers showed any manifestations of PCB toxicity. When compared to five controls matched for sex, age, and smoking and drinking habits, the antipyrene half-life was about 2/3 of the control level (10.8 ± 0.7 experimental vs. 15.6 ± 1.0 control). The increased rate of antipyrene clearance was taken to be an indication of higher levels of metabolic enzymes in the livers of the exposed workers.

Data from this limited review of occupational studies indicate that symptoms much like those seen after PCB ingestion can occur after atmospheric or dermal exposure. Air PCB concentrations as low as 0.1 mg/m^3 can produce toxic effects (Meigs, 1954) and exposure to levels producing no overt toxicity can affect liver function (Alvares, et al. 1977). Recovery after termination of exposure occurs but is slow and depends upon the amount of PCBs stored in adipose tissue (Natl. Inst. Occup. Safety Health, 1977).

Synergism and/or Antagonism

It appears that the synergistic antagonistic effects of PCBs result from their ability to induce mixed function oxidases in liver and other tissues, although the effects of the accelerated metabolism of drugs, such as phenobarbitol or hormones, such as ketosteroids and thyroxin, have been discussed above. The consequences of the PCB induced metabolism of carcinogenic agents such as benzene hexachloride or aflatoxin will be discussed below in the section on carcinogenicity.

Teratogenicity

The reproductive effects of PCBs in animals and man have been discussed above. It is clear that PCBs readily cross the placental barrier and accumulate in fetal tissues. Primate infants exposed to PCBs *in utero* are typically retarded in growth during gestation (Barsotti and Allen, 1975) and reproductive failures (abortions, stillbirths) are common (Linder, et al. 1974). Live born animal and human infants often display symptoms of toxicity common for the species (Kuratsune, et al. 1976; Linder, et al. 1974). However, indications of structural malformations or genetic changes have been rare. Villeneuve, et al. (1971b) noted assymetric skull formation in two rabbit fetuses exposed to high levels of Aroclor 1254 _in utero_. A written communication by F.L. Earle (as cited in Natl. Inst. Occup. Safety Health, 1977) reported unspecified terata in canine pups born to females exposed to 48 or 200 ppm but not 20 ppm dietary equivalent, and in piglets from sows fed the equivalent of 50 ppm. No additional information was given.

Mutagenicity

The mutagenicity of different PCB preparations has been evaluated in several test systems. The single isomer 4-chlorobiphenyl was found to be highly mutagenic in _Salmonella typhimurium_ strain TA1538 after liver microsomal enzyme activation (Wyndham, et al. 1976). The products formed under these activation conditions were 4 chloro-4'-biphenylol and 4'chloro- 3, 4 biphenyldiol, which, as previously discussed, are indicative of arene oxide formation (Safe, et al. 1975). In the same study, Aroclor 1221 was less mutagenic while Aroclor 1254, 1268 and 2, 5, 2', 5' tetrachlorobiphenyl were essentially inactive. Mutagenic activity decreased with increasing chlorination.

Recent attempts to repeat the experiment with different cultures of the same tester strain have not detected any mutagenic activity (S. Safe, personal communication).

Also 4-chlorobiphenyl was toxic but not mutagenic to _S. typhimurium_ TA 1538 with or without activation by Aroclor

1254 (S. Rinkus, personal communication). 4-chlorobiphenyl has been shown to induce unscheduled DNA synthesis, an indication of DNA repair, in Chinese hamster ovary cells (S. Safe, personal communication).

The Japanese Ministry of Health and Welfare supported mutagenicity screening program investigated Kanechlors 300 and 500 (Odashima, 1976). Both compounds were negative in the _Salmonella_ system but Kanechlor 300 was listed as positive in a bacterial DNA repair assay and a cytogenetic analysis with Yoshida sarcoma cells. Kanechlor 500 was positive in a mouse bone marrow cell cytogenetic analysis.

Heddle and Bruce (1977) reported Aroclor 1254 as negative in _S. typhemurium_, the micronucleus test and a sperm morphology assay. Aroclor 1254 administered to rats at 50 mg/kg/day for seven days produced no chromosomal abnormalities in sperm (Dikshith, et al. 1975).

The effects of Aroclor 1254 and 1242 on bone marrow cells were evaluated in Osborn-Mendel rats (Green, et al. 1975a). Animals in groups of eight were given single doses of Aroclor 1242 at 1250, 2000, or 5000 mg/kg or multiple doses of 500 mg/kg/day for four days. Aroclor 1254 was given for five days at 75, 150, or 300 mg/kg/day. Aroclor 1242 was more toxic than 1254. Mitotic indices were not reduced by Aroclor 1242 treatment and no increase in chromosomal abnormalities was observed. Aroclor 1254 reduced the mitotic index of bone marrow cells at 150 and 300 mg/kg/day but not at the low dose. Again, no increase in chromosomal abnormalities was seen. Cytogenetic abnormalities were found in spermatogonial cells of animals treated at 5000 mg/kg or 500 mg/kg/day Aroclor 1242 but not in statistically significant numbers.

A dominant lethal test with Aroclor 1242 and 1254 was also performed in Osborne-Mendel rats (Green, et al. 1975b). Aroclor 1242 was given in single doses of 625, 1250, or 2500 mg/kg or five doses of 125 or 250 mg/kg/day. Aroclor 1254 was given in five doses of 75, 150, or 300 mg/kg/day. Treated males were bred to untreated females for the following 10 to 11 weeks. No significant effect of treatment was observed on embryo implantation or lethality with any treatment.

In summary, the only marked genetic effect observed at any level was with the single isomer 4-chlorobiphenyl. Kanechlor 300 and 500 produced cytogenetic effects in different systems but Aroclor 1242 and 1254 did not. Despite the apparent weak mutagenicity of most PCBs in the systems used, the fact that most animals can metabolize many PCB isomers through an arene oxide intermediate indicates that the mutagenic potential of PCBs should not be casually dismissed.

Carcinogenicity

The carcinogenic effects of PCBs have been evaluated in several animal studies. The first evidence of carcinogenic potential in PCBs was reported by Nagasaki, et al. (1972) and in more detail by Ito, et al. (1973). Male dd mice were given Kanachlors 500, 400, and 300 mixed in standard diets at 500, 250, and 100 ppm for 32 weeks. Of 12 mice surviving in the group fed 500 ppm Kanachlor 500, 7 (58.3 percent) had grossly observable nodular hyperplasia with microscopically observable hepatomas in 5 (41.7 percent). No tumors were observed in the groups treated with lower doses of Kanechlor 500, in any dose of the other Kanechlors, or in the six control animals. Kimbrough and Linder (1974) treated Bald/cJ mice with Arochlor 1254. Mice were exposed to 300 ppm in the diet for 6 or 11 months. The mice exposed for six months were fed control diets for the remaining five months, and all the animals were killed and examined at the same time. All the animals surviving 11 months exposure had enlarged livers and adenofibrosis, while 9/22 (41 percent) were observed to have hepatomas. Of the 24 mice surviving six months exposure, most showed some changes in liver cell morphology, and a diffuse interstitial fibrosis was observed in about 2/3 of them. One hepatoma (0.3 cm diam.) was observed. The details of the mouse experiments are summarized in Table 10. Kimbrough and Linder (1974) reported subcutaneous abcess formation in some mice and one sweat gland adenoma. Neither Ito, et al. (1973) nor Nagaski, et al. (1972) commented on any pathology other than in the liver.

Studies with rats have been reported by Kimura and Baba (1973), Kimbrough, et al. (1972, 1975), and Ito, et al. (1974). Kimura and Baba (1973) examined the effects of Kanechlor 400 on the livers of Donryu strain rats. Ten male and ten female animals were exposed, in a complex protocol, to amounts of Kanechlor 400 starting at 38.7 ppm in food and increasing to 616 ppm as the animals increased in weight. Total amounts ingested varied from 450 to 1500 mg over exposure periods of 159 to 560 days. Five control animals of each sex were used. Fatty degeneration was observed in the livers of all experimental animals and two females in the control group. Adenomatous nodules were observed in all of the

TABLE 10

Evidence for Carcinogenic Effects of PCB's in Mice.

Mouse Strain	Sex	No. Treated	No. Surviving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Liver Nodules			
								Adenofibrosis	Neoplastic Nodules	Hepatoma	Hepatocellular Carcinoma
dd (Ito, et al. 1973; & Nagasaki et al. 1972)	M	12	12	Kanechlor 500	500	82.5^a	224	-	7/12		5/12
		12	12	"	250	41.3^a		-	0/12		0/12
		12	12	"	100	16.5^a		-	0/12		0/12
				Kanechlor 400	500	82.5			0/12		0/12
				"	250	41.3			0/12		0/12
				"	100	16.5			0/12		0/12
				Kanechlor 300	500	82.5			0/12		0/12
					250	41.3			0/12		0/12
		6	6	Control	100	16.5			0/6		0/6
Balb/cJ (Kimbrough & Linder, 1974)	M	50	22	Aroclor 1254	300	49.8	330	22/22	-	9/22	
		50	24	"	300	49.8^b	180^c	0/24	-	1/24	
		100	58	"	-	-	-	0/58	-	0/58	

[a] Calculated using food consumption data from Kimbrough and Linder (1974) for Balb/cJ mice which indicates an average of 165 g/kg/day.

[b] Not directly, but assumed to be similar to group exposed 330 d.

[c] Maintained on control diet for remaining 150 days of experiment.

females which had a cumulative intake of more than 1200 mg Kanechlor 400. Nodules were seen in none of the males. A number of histopathological findings were noted in spleen, lung, adrenal cortex, and brain but no neoplastic changes outside the liver were mentioned.

Ito, et al. (1974) examined the effects of Kanechlors 500, 400, and 300 on male Wistar rats. Animals were exposed to dietary levels of 1000, 500, and 100 ppm of each preparation for 27 to 52 weeks, then killed and examined for pathological changes. No hepatocellular carcinoma was observed, but cholangiofibrosis (adenofibrosis) was seen at the highest dose of all three agents (Table 11). Nodular hyperplasia was observed in animals treated with all three agents. The highest incidence was observed with Kanechlor 500. No significant changes were observed in organs other than the liver.

Kimbrough, et al. (1975) exposed Sherman strain rats to Aroclor 1260 at dietary levels of 100 ppm for 21 months. Hepatocellular carcinomas were observed in 26/184 experimental animals but in only one of the controls (1/173). Tumors were observed in several other tissues of both experimental and control groups, but they were of low incidence and frequencies were similar in both groups. In an earlier study, Kimbrough, et al. (1972) fed Aroclor 1254 and 1260 to male and female rats for eight months. Adenofibrosis was observed in animals fed 100 and 500 ppm Aroclor 1254 with the highest incidence in females. Aroclor 1260 was associated with a much lower incidence of adenofibrosis even in animals fed 1000 ppm. A single bladder tumor was observed in a

TABLE 11

Evidence for Carcinogenic Effects of PCB's in Rats

Strain	Sex	No. Treated	No. Surviving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Adenofibrosis	Liver Nodules: Neoplastic Nodules	Liver Nodules: Hepatocellular Carcinoma
Donryue (Kimura and Baba, 1973)	M	10	10	Kanechlor 400	38.5-16	13.5[c]	339[a]	-	0/10	-
	F	10	10	Kanechlor 400	38.5-16	17.5[d]	425[b]	-	6/10	-
	M	5	5	None	-	-	-	-	-	-
	F	5	5	None	-	-	-	-	-	-
Wistar (Ito, et al. 1974)	M	*	13	Kanechlor 500	1000	49.0[e]	378	4/13	5/13	-
			16	"	500	24.5		0/16	5/16	-
			25	"	100	4.9		0/25	3/25	-
			10	Kanechlor 400	1000	49.0		2/10	3/10	-
			8	"	500	24.5		0/8	0/8	-
			16	"	100	4.9		0/16	2/16	-
			15	Kanechlor 300	1000	49.0		2/15	0/15	-
			19	"	500	24.5		0/19	0/19	-
			22	"	100	4.9		0/22	1/22	-
			18	None	0	-	-	0/18	0/18	-

Table 11 (Cont.)

Strain	Sex	No. Treated	No. Sur-viving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Proliferative Changes: Nodular Hyperplasia	Proliferative Changes: Hepatocellular Carcinoma and Adenoma	Proliferative Changes: Combined Hematopoietic and Liver
Fisher 344 rat (NCI, 1978)	M	25	24	Aroclor 1254	0	0	-	0/24	0/24	5/24
			24		25	1.38^{e}	735	5/24	0/24	2/24
			24		50	2.75^{e}	735	8/24	1/24	9/24
			24		100	5.5^{e}	735	12/24	3/24	12/24
	F	25	23		0	0	-	0/23	0/23	4/23
			24		25	1.38^{e}	735	6/24	1/24^{g}	13/24
			22		50	2.75^{e}	735	9/22	1/22	8/22
			24		100	5.5^{e}	735	17/24	2/24	9/24

Table 11 (Cont.)

Strain	Sex	No. Treated	No. Sur-viving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Liver Nodules		
								Adeno-fibrosis	Neoplastic Nodules	Hepatocellular Carcinoma
Sherman (Kimbrough, et al. 1975)	F	200	184	Aroclor 1260	100	4.9[f]	630	-	144/184	26/184
	F	200	174	None	-	-	630	-	0/173	1/173
Sherman (Kimbrough, et al. 1972)	M	10	10	Aroclor 1260	1000	71.4	240	2/10	-	-
	F	10	10	"	100	7.2		1/10	-	-
		10	8	"	500	38.2		1/9	-	-
		10	2	"	1000	72.4		4/7	-	-
	M	10	10	Aroclor 1254	100	6.8		1/10	-	-
		10	10	"	500	36.4		10/10	-	-
	F	10	10	"	100	7.5		7/10	-	-
		10	9	"	500	37.6		9/9	-	-

[a] range 159-530

[b] range 244-560

[c] range of cumulative intake 450-1800 mg

[d] range of cumulative intake 700-1500 mg

[e] Data not provided. Calculated from Kimbrough, et al. 1975, in which Sherman rats showed similar weight gain over the same experimental period.

[f] Time weighted average calculated from Figure 2 in Kimbrough, et al. 1975.

[g] Reported as undifferentiated carcinoma of the liver, metastatic.

*290 animals total in 10 groups

treated animal but was probably not the result of PCB exposure (Kimbrough, et al. 1975). The details of the experiments with rats are summarized in Table 11.

A report dated November, 1971 described a study made by Industrial Bio-test Laboratories Inc. A brief summary of the report was presented at the National Conference on Polychlorinated Biphenyls (1976) and a more detailed analysis presented by the U.S. EPA (1976a). One thousand Charles river rats were divided into ten treatment groups. Fifty male and 50 female rats served as a common control group. Each of nine treated groups contained 50 animals of each sex. Groups were fed 1, 10 and 100 ppm of Aroclors 1242, 1254, and 1260 respectively. Treatment was initiated with four to six week old animals and continued for a total of 24 months. Five animals of each sex were sacrificed at 3, 6, and 12 months leaving 35 animals in each group at the beginning of the second year. In addition, mortality was high, leaving only 6 to 21 animals remaining in each treatment/sex subgroup by the end of the experiment. As seen in the previously described studies, the principal effects were observed in the liver. Vacuolar changes and hyperplasia were the major abnormalities originally noted in the treated animals. In addition chromophobe adenomas of the pituitary were found in 8 of 9 treated groups but not in the controls. In 1975 the original liver slides were re-evaluated with rather different results. The combined results for animals treated with 100 ppm of all three Aroclors included 11 hepatomas, 5 cholangiohepatomas, and 28 nodular hyperplasias. No hepatocellular carcinomas were observed.

Recently, a bioassay for the possible carcinogenesis of Aroclor 1254 has been conducted by the National Cancer Institute (1978). In this study, 24 Fischer 344 rats of each sex were orally administered Aroclor 1254 at 25, 50, or 100 ppm for 104 to 105 weeks. Matched controls consisted of 24 untreated rats of each sex. Mortality among the treated males was significantly higher than among the controls and related to dose ($P < 0.001$) but was not different among the females ($P > 0.05$). Interstitial-cell tumors of the testes in males and leukemias of either granulocytic or lymphocytic type were observed frequently in both control and treated animals. Tumors were observed in several other tissues but their presence did not correlate with treatment. Proliferative lesions of the liver were common in treated animals but were not found in controls. The types and frequencies of lesions are detailed in Table 11. They included nodular hyperplasia in all treated groups increasing in frequency with dose, adenomas (one male, three females) and hepatocellular carcinoma (three males, no females). In addition, adenocarcinomas of the stomach, jejunum or cecum of two treated males and two treated females but no controls were observed. Statistical analysis of the frequencies of tumors and proliferative lesions indicated that the combined incidences of leukemia and lymphoma in treated males were significant by one test (Cochran-Armitage test for positive dose-related trend) but not by a more stringent test (Fisher exact test). The tumors of the liver and gastrointestinal tract were not statistically significant; however, the occurrence of nodular hyperplasia appeared to be related to treatment.

The study concluded that Aroclor 1254 was not carcinogenic in Fischer 344 rats; however, the high frequency of hepatocellular proliferative lesions was considered to be a result of treatment, and the carcinomas of the gastrointestinal tract possibly associated with the treatment.

The tumors observed in rodent experiments with PCBs were predominantly adenofibrosis (cholangiofibrosis) neoplastic nodules and hepatocellular carcinomas. Stewart and Snell (1957) concluded that adenofibrosis cannot be considered to be a pre-malignant lesion, while Reuber (1968) proposed that cholangiofibrosis might be a precursor to cholangiocarcinoma. Neoplastic nodules have been observed before the appearance of carcinomas in several studies with known carcinogens (Kimbrough, et al. 1975). Well-differentiated mouse hepatomas have been shown to be potentially malignant, with a proportion being transplantable and capable of metastasis (Andervant and Dunn, 1952).

Several conclusions can be drawn from the results of the rodent studies. A correlation between degree of chlorination and tumor inducing potential was observed in mice (Ito, et al. 1973) and rats (Ito, et al. 1974) with the most highly chlorinated preparations being most potent. However, Aroclor 1254 was more potent than Aroclor 1260 in rats (Kimbrough, et al. 1972). Where examined, female rats were found to be more sensitive than males (Kimura and Baba, 1973; Kimbrough, et al. 1972). No comparisons of sex-related effects were made in mice.

It should be noted that none of these studies was a lifetime study. In all cases, animals were treated for fixed times then killed and examined. No lifetime studies with PCBs were found in this survey. Such studies, if available, might indicate more clearly the significance of the potentially preneoplastic lesions induced by PCBs in the studies described here.

Data on the possible carcinogenicity of PCBs in humans are sketchy at this time. The largest group of exposed individuals followed longitudinally are the "Yusho" patients. By late 1973, 2 of 1291 patients had died, 9 of them with malignant neoplasms (2 stomach cancer, 1 stomach and liver cancer, 1 liver cancer with cirrhosis, 1 lung cancer, 1 lung tumor, 1 breast cancer, and 1 malignant lymphoma) (Urabe, 1974; Kuratsune, et al. 1976). The authors did not have sufficient information to make a detailed epidemiological analysis but concluded that 9/22 deaths from cancer may represent an excess of deaths.

Two cases of malignant melanoma were reported in a group of 31 industrial workers exposed "heavily" to Aroclor 1254 in the process of its manufacture. Based on a person-year analysis and the use of the Third National Cancer Survey incidence rates (Natl. Cancer Inst. 1978), 0.04 malignant melanomas would have been expected making these data significant at the 0.001 level. In addition, one of 41 workers exposed to lower levels of Aroclor 1254 developed a malignant melanoma (Bahn, et al. 1976).

Although these studies involve small numbers of individuals and provide little information about exposure or other relevant factors, they do suggest that human exposure to PCBs may be associated with increased risk of neoplasia.

In addition to the carcinogenic effects observed with PCBs, they have been shown to have a significant effect on the carcinogenic properties of other substances found in the environment. The co-carcinogenic properties of the PCBs result from their ability to induce the mixed function oxidases, particularly in liver, as discussed under Acute, Sub-acute,and Chronic Toxicity. Ito, et al. (1973) observed that dietary levels of 250 ppm Kanechlor 500 markedly promoted hepatocellular carcinoma and nodular hyperplasia in mice exposed to benzene hexachloride at levels of 100 or 250 ppm in the diet. Kanechlor 400 at 10 or 100 ppm in the diet failed to promote cervical carcinoma or progression toward it in mice exposed to 20 methyl cholanthrene saturated thread implanted in the cervix and uterus (Uchiyama, et al. 1974). Ito, et al. (1978) observed a pronounced increase in the incidence of preneoplastic, hyperplastic nodules in N-2-fluorenylacetamide treated rats. The animals were fed 1000 ppm PCB (type not specified) for eight weeks following two weeks exposure to the carcinogen. This increase in preneoplastic lesions over a short period was taken to be a significant indicator of carcinogenic activity. The ability of Aroclor 1254 to initiate (as opposed to promote) tumors in the two-stage mouse skin system was recently examined by DiGiovanni, et al. (1977). Aroclor 1254 proved to be a weak initiator of papillomas when a 100 ug treatment of skin was followed by 32 weeks of treatment with the promotor 27 tetradenanoyl-phorbol-13' acetate. When used in combination with the potent initiator dimethylbenzanthracene Aroclor 1254 slightly increased the incidence of papillomas. Aroclor

1254 also failed to promote skin tumors initiated by dimethylbenzanthracene in the same system (100 µg Aroclor 1254 applied twice weekly for 30 weeks) (Berry, et al. 1978).

Kanechlor 500 promoted hepatocellular carcinoma initiated by diethylnitrosamine (DENA) in male Wistar rats (Nishizumi, 1976). Promotion was observed when PCB treatment was begun one week following the end of DENA treatment. The number of tumors was significantly higher in rats treated with DENA and PCB than DENA alone or DENA and phenobarbital although a promoting effect was observed with the latter drug as well.

Hepatocarcinogenesis initiated by 3'-methyl - 4-dimethylaminoazobenzene (3'-Me-DAB) in female Donryu strain rats was promoted by oral administration of PCBs following initiation. Tumor incidences in animals treated with 3'-Me-DAB + PCB, 3'-Me-DAB alone, or PCB alone were 64 percent, 13 percent, and 0 percent, respectively. PCB treatment preceding or simultaneous with 3'-Me-DAB treatment did not produce tumors (Kimura, et al. 1976).

By contrast to the hepatic co-carcinogenic effects of PCBs observed by Kimura, et al. (1976), Nishizumi (1976), and Ito, et al. (1973; 1978), other investigators have observed an inhibition of tumor formation or growth in the presence of PCBs. Makiura, et al. (1974) fed male Sprague Dawley rats 3'-Me-DAB, 2FAA, or DEN or pairwise combinations of them for 20 weeks followed by 4 weeks on a stock diet. Incidence of hepatocellular carcinoma ranged from 65.2 to 92.3 percent, and nodular hyperplasia reached 100 percent in animals fed pairs of carcinogens. The addition of 50 ppm Kanechlor 500 to the diet resulted in a large decrease in the tumor incidence and liver weight as compared to carcinogen treatment without PCBs. PCBs alone induced no tumors or hyperplastic nodules but did result in an increased liver weight. The principal difference between this study and those of Ito, et al. (1978), Nishizumi (1976), and Kimura, et al. (1976) using the same chemicals is that PCB exposure was delayed until after the initiating treatment in the latter studies. This suggests that the induction of mixed function oxidases by PCB at the time of carcinogen treatment results primarily in the inactivation of the chemicals and that the promoting effects observed with sequential exposure result from some other mechanism. The co-carcinogenesis of PCBs with simultaneous exposure to BHC may reflect a difference in the liver metabolism of this compound.

In rainbow trout (Salmo gairdnerii) 100 ppm Aroclor 1254 added to the diet reduced the size and frequencies of liver tumors induced by 6 ppm aflatoxin B_1 after a one year exposure (Hendricks, et al. 1977).

In addition to the inhibition of tumor induction by some chemicals, PCBs were also shown to inhibit the growth of experimental tumors in rats. Sprague-Dawley rats were inocculated with Walker 256 Carcinosarcoma cells and the effects of PCBs determined. Both dietary (Kerkvliet and Kimeldorf, 1977a) and injected (Kervliet and Kimeldorf, 1977b) Aroclor 1254 reduced the size of solid tumors and increased animal lifespan. Total dietary PCB intake of 1100 to 2000 mg/kg over a 40-day period reduced tumor weight to 60 to 40 percent of control in both male and female rats. Aroclor 1254 injected i.p. reduced the efficiency of tumor takes when 10^3 tumor cells were injected from 81.3 in control to 50.0 percent in animals receiving 200 mg/kg/day. Mean tumor sizes were reduced and lifespans increased by PCBs in animals inocculated with 10^7 tumor cells. Administration of PCBs for five days preceding tumor inoculation or the first five days after inoculation was more effective than administration between days five and ten.

CRITERION FORMULATION

Existing Guidelines and Standards

The Toxic Substances Control Act (TSCA) (P.L. 94-469) was signed into law October 11, 1976. Provisions in section 6(e) of the law specifically regulate the manufacture, sale, distribution, and disposal of PCBs. Manufacture, sale, or distribution of PCBs was restricted to sealed systems as of October 11, 1977. Manufacture was banned as of January 1, 1979 and all processing and distribution in commerce will cease July 1, 1979. Allowance for certain exemptions is provided in the law. The proposed rules to implement the terms of section 6(e) of TSCA were released June 7, 1978 (U.S. EPA, 1978b). Proposed rules on the disposal of PCBs were released February 17, 1978 (U.S. EPA, 1978a). The Environmental Protection Agency has proposed a water quality criterion for the protection of fresh water and marine life of 0.001 ug/l (U.S. EPA, 1976b). The Food and Drug Administration established tolerance levels in foods in 1973 (38 FR 18096) and proposed new tolerance levels further restricting levels in 1977 (42 FR 17487). Both the current allowed levels and the proposed levels are presented in Table 3.

The occupational exposure limits adopted in 1968 are based on the recommendations of the American Conference of Governmental Industrial Hygienists (ACGIH) (1968). They set the time-weighted average eight hour exposure limits to 1.0 mg/m^3 for mixtures containing 42 percent chlorine and .5 mg/m^3 for mixtures containing 54 percent chlorine.

The newly recommended standard proposed by NIOSH (1977) is 1.0 ug/m^3 air TWA over a 10-hour day and 40-hour work week.

Current Levels of Exposure

Human exposure to PCBs in the United States has been broad. Several studies of tissue and plasma levels of PCBs have detected them in a high percentage of randomly chosen subjects. Yobs (1972) detected PCBs in 31.1 percent of 637 human adipose tissue. The National Human Monitoring Program for Pesticides in fiscal years 1973 and 1974 found PCBs in 35.1 and 40.3 percent of adipose tissues tested (Kutz and Strassman, 1976). Table 12 indicates the distribution of PCB concentrations in the population. A study of Canadian human adipose tissue PCB levels found 1 ppm or more in 30 percent of 172 samples (Grant, et al. 1976). The eastern provinces, particularly Ontario, had the highest incidences. Average adipose tissue PCB levels were just below 1 mg/kg (ppm) with males having slightly higher accumulations than females. The same study found human breast milk to contain about 1 mg/kg on a fat basis. PCBs were detected in 8 of 40 samples of breast milk in Colorado at levels between 40 and 100 ppb (whole milk). The Japanese study described earlier found average levels in 400 milk samples of about 30 ppb (Yakushiji, et al. 1977). PCB levels in plasma in U.S. populations were detected in 43 percent of 723 samples. Levels in positive samples ranged from 1.5 to 29 ppb with a mean around 2 to 3 ppb. White populations had higher levels than black populations (Finklea, et al. 1972).

TABLE 12

Levels of Polychlorinated Biphenyls in Human Adipose Tissue

Data source	Sample size	Percent nondetected	Percent 1 ppm	Percent 1-2 ppm	Percent 2 ppm
Yobs, 1972	688	34.2	33.3	27.3	5.2
FY 1973 Survey	1277	24.5	40.2	29.6	5.5
FY 1974 Survey	1047	9.1	50.6	35.4	4.9

From: Kutz and Strassman (1976)

As discussed in the section on exposure, the median water levels of PCBs are around 0.1 to 0.3 µg/l in positive samples with 0 to 20 percent of samples being positive around the U.S. (Dennis, 1976). Average PCB intake in food was estimated in the mid-1970's to be about 9 µg/day with fish being the major dietary source. Ambient air concentrations are around 100 ng/m^3 (Kutz and Yang, 1976).

Special Groups at Risk

The preceding discussion of human exposure makes clear the fact that a high percentage of the U.S. population has been and is exposed to low levels of PCBs in food, water, and air. Those groups at particular risk for PCB exposure include industrial workers exposed in the workplace, individuals consuming large amounts of contaminated fish, such as sport fisherman (42 FR 17487), and nursing infants who, per kg body weight, may accumulate significant body burdens from the levels in human breast milk. With the cessation of manufacture of PCBs by Monsanto in 1977 and the great decline in its use which should result from the implementation of section 6(e) of TSCA, industrial exposure should decline substantially. Since many PCB-containing sealed systems can be expected to remain in service for many years continuing vigilance will be necessary to minimize accidental pollution of waterways or air and to prevent further occupational exposure.

Basis and Derivation of Criterion

In arriving at a criterion for PCB levels in ambient waters several factors must be taken into account. First, PCBs are highly persistent in the environment and accumulate to a high degree in food webs. As discussed in the section Ingestion from Foods, an average bioaccumulation factor for PCB's in all freshwater fish and shellfish of 46,000 has been determined. As a consequence, PCBs leave the environment very slowly once they have entered it. Not only do PCBs persist and accumulate in the environment but in man as well. The current environmental levels are not producing obvious acute ill health in the general population. However, several animal studies report that PCBs produce a carcinogenic response and that they may enhance the carcinogenic activities of other substances.

Although other adverse effects of PCB exposure could be used as a basis for formulating a criterion, carcinogenicity will be used for a variety of reasons. The most extensive chronic studies with PCBs have identified carcinogenicity as the major end point. Although no carcinogenicity studies have been extended to more than one generation and firm data exist only for the female rat, a credible carcinogenic response to PCBs has been demonstrated and cannot be ignored. Kimbrough, et al. (1972) observed an incidence of hepatocellular carcinoma of 26/184 in treated rats compared to 1/173 in controls. The NCI bioassay observed a similar frequency of hepatocellulor carcinoma at a similar dose level which was statistically not significant because the number of animals was low. In addition, a number of non-mali proliferative processes observed in liver at high frequencies in the PCB treated animals in these studies were also observed in both rats and mice in other studies (Ito, et al. 1974; Kimura and Baba 1973; Kimbrough, et al. 1972; Ito, et al. 1973; Kimbrough and Linder, 1974). PCBs were classified as carcinogenic by the International Agency for Research on Cancer (IARC, 1974). Evidence from human populations suggests but does not confirm an increase in cancer frequency due to PCB exposure (Kuratsune, et al. 1976; Bahn, 1976). Finally, a theoretical basis exists for the quantitative extrapolation of carcinogenic effects in treated animals to human populations. Various models, such as the one used below, can provide quantitative risk estimates based on animal data, and certain assumptions about the induction of neoplasia (e.g. one-hit or multi-hit induction). No basis exists for extrapolation with mathematical models from animals to man for many other kinds of biological effects.

Although the criterion established below is based on animal carcinogenicity data it should also be noted that other adverse effects have been observed in mammals at levels below the dose which produces tumors in rats. The carcinogenic effect was observed in rats consuming an average of 4.9 mg/kg/day. Dietary levels at 2.5 ppm produced adverse reproductive effects in Rhesus monkeys (Allen and Barsotti, 1976). If a food intake of 350 g/day is assumed, the PCB dose is 146 ug/kg/day in 6 kg animals. At this time no data are available to indicate the minimal level in the diet at which PCBs produce toxic effects in Rhesus monkeys.

In mink, ingestion of as little as 61 mg of Aroclor 1254 over nine months or 90 mg of Aroclor over four months resulted in sharply reduced reproduction (Aulerich and Ringer, 1977). Assuming a weight of 1 kg for adult mink and a food intake of 150 g/day, the PCB dose at 2 ppm was about 300 ug/kg/day which is similar to the level producing reproductive toxicity in monkeys.

These data can be used in one approach to developing an ambient water quality criterion. If 300 µg/kg/day is taken as the lowest-observable-effect-level (LOEL) than an Acceptable Daily Intake (ADI) can be calculated for a 70 kg man using an uncertainty factor of 100:

$$\frac{300 \times 70}{100} = 210\ \mu g/day$$

Assuming that exposure to PCBs is based on the consumption of 2 liters of drinking water, 18.7 grams (0.0187 kg) of fish and shellfish, and a bioconcentration factor of 46,000; then the following calculation can be made:

$$(2\ \text{liters})\ X + (0.0187 \times 46{,}000) = 210\ \mu g$$

$$X = .244\ \mu g/l$$

$$\text{or } 244\ ng/l)$$

As will be seen later, the carcinogenicity criterion methodology gives a lower and presumably more cautionary level.

An assessment of carcinogenic risk will be made by extrapolation from animal data using a linear (non-threshold) model. The model used takes into account the bioaccumulation of PCBs in fish and shellfish. It is assumed that an average of 2 liters/day of water are consumed along with 18.7 g of fish taken from that water source. Exposures from other food sources, air or occupational exposure are not included in the criterion level derived by this model.

Among the studies reviewed by this document, only one appears suitable for use in the cancer risk assessment. None of the mouse studies involved feeding for most or all of a lifetime and are therefore unsuitable. Of the rat studies, the only one involving long term exposure and adequate numbers of animals is the study of Sherman rats by Kimbrough, et al. (1975).

This study has some drawbacks in that it lacks any evidence of a dose-response (due to the use of only one dose level), it tests only one sex of the species, and only one commercial mixture of PCBs was tested. Yet the experimental design is a good one in many ways: the treatment was given over a good proportion of the lifespan; there was an appropriate route (food) and distribution of exposure (uniform dose over time); the authors provided good documentation of the actual intake dose; a sufficiently large number of experimental and control animals were used to detect a statistically significant increase in tumors; and there was a thorough and well documented description of the pathology (hepatocellular carcinoma). The NCI study (1978) was the only other study involving a long-term exposure and was suggestive of a carcinogenic effect; however, the lack of an adequate number of animals renders it unsuitable as a study upon which to base an estimate of carcinogenic risk.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organims, human health, and recreational activities." PCBs are suspected of being human carcinogens. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of PCBs in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentration of PCBs corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2).	0	0.0026 ng/l	0.026 ng/l	0.26 ng/l
Consumption of fish and shellfish only.	0	0.0026 ng/l	0.026 ng/l	0.26 ng/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in FR 15926, 1979. Appropriate bioassay data used in the calculation are presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying of dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 99.8 percent of the PCB exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 46,000 fold. The remaining 0.2 percent of PCB exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of PCBs, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding PCB's concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding PCB concentrations. although total exposure information for PCBs is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

These criteria are exceedingly low. Although sharp restriction of open PCB use in 1970 resulted in notable declines in water PCB levels in the next several years (Dennis, 1976), the residual levels remaining are still two to three orders of magnitude above the extrapolated level indicated by the model. The major source of PCBs in water today is probably not new effluents from industrial or domestic sources, but the PCB containing sludges underlying waterways which typically contain 100 to 1000 fold higher concentrations than the water itself (Dennis, 1976). Efforts to reduce water levels significantly by eliminating current pollution sources will probably have little effect on average water PCB concentrations.

The very low limits suggested by this risk estimate are due in large part to the very large bioaccumulation factor in fish (46,000). This figure is an average for a wide variety of saltwater and freshwater organisms (see section on Ingestion from foods).

As possible strategies to reduce human exposures to PCBs are considered, the relative contributions of ingested water and fish should be kept in mind. At the assumed consumption rate of 2 l of drinking water and 18.7 g of fish/day, over 99 percent of the dietary PCBs will be obtained from fish. Strategies which focus separately on the reduction of PCB levels in water and fish for human consumption might be more practical and productive than a single standard for water which takes bioaccumulation in fish into account.

A final comment about the risk level derived from this study is that it is based on animal data which are [illegible] histically weak. The weight of evidence indicates that PCBs are carcinogenic in rodents. However, the carcinogenic activities of these compounds are not great. An acceptable noncarcinogenic level could be established with greater certainty if better quantitative data on carcinogenicity were available. Studies with larger numbers of animals designed to measure relatively small effects are needed. Also, the rat appears to be much less sensitive to the acute and subacute effects of PCBs than man or non-human primates. Further investigation of the effects of PCBs in Rhesus monkeys, particularly with reference to the gastric lesions produced, would be useful.

APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Polychlorinated Biphenyls*

Polychlorinated biphenyls (PCBs) are prepared by the chlorination of biphenyl and are complex mixtures containing isomers of chlorobiphenyls with different chlorine content.

Because of the widespread industrial use of PCBs, their long half-life, and the documented disease-producing capability of these compounds in several species, regulations have been promulgated banning most of the manufacturing, processing, and distribution of PCBs in the United States (FEDERAL REGISTER Vol. 44, No. 106, May 31, 1979).

Human studies concerning the possible carcinogenicity of PCBs have involved small numbers of individuals and provide little information about exposure. Although these studies are only marginally useful in describing the carcinogenicity of PCBs, the incidence of malignant neoplasms in "Yusho" patients and in industrial workers exposed to Aroclor 1254 suggests that human exposure to PCBs is associated with an increased risk of neoplasia.

In two separate studies, PCBs have been reported to induce hepatocellular carcinomas in both mice and rats (male mice fed Kanechlor 500 at 500 ppm and female Sherman rats fed Aroclor 1260 at 100 ppm).

In an NCI bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats, but the high frequency of hepatocellular proliferative lesions was considered to be the result of treatment and carcinomas of the gastrointestinal tract possibly associated with treatment. In one other mouse study and three other rat studies, various PCBs induced proliferative lesions of the liver which might be indicative of carcinogenicity. The most commonly seen lesions were adenofibrosis (cholangiofibrosis) and neoplastic nodules.

A correlation between degree of chlorination and tumor inducing potential was observed in both mouse and rat species. The most highly chlorinated preparations were also the most potent tumor inducers with the exception of Aroclor 1254 which was more potent than Aroclor 1260 in one rat study. Where examined, female rats were found to be more sensitive than males. No comparisons of sex related effects were made in mice.

PCBs have been reported to be co-carcinogens, initiators, and promotors in both mouse and rat species.

The mutagenicity of different PCB preparations has been evaluated in several test systems with conflicting results. In one study, the single isomer 4-chlorobiphenyl was reported to be highly mutagenic in *Salmonella typhimurium* strain TA 1538 after liver microsomal activation, while Aroclor 1221 was reported to be less mutagenic and Aroclors 1254, 1268, and 2,5,2',5'-tetrachlorobiphenyl were inactive. The fact that mutagenic activity decreased with increasing chlorination is consistent with the characteristic insensitivity of the ames test to chlorinated hydrocarbons. In other test systems, Kanechlor 300 inhibited bacterial DNA repair deficient cells and induced cytogenetic abnormalities in Yoshida sarcoma cells. Kanechlor 500 tested positive in a mouse bone marrow cytogenetic analysis.

In summary, carcinogenic responses have been induced in mice and rats. These results, together with positive mutagenic responses, and suggestive epidemiologic evidence, constitute substantial evidence that PCBs are likely to be human carcinogens.

The water quality criterion for PCBs is based on the Kimbrough, et al. (1975) study on the induction of hepatocellular carcinomas and neoplastic nodules in female Sherman strain rats fed 100 ppm Aroclor 1260. It is concluded that the water concentration of PCBs should be less than 0.26 ng/l ($\sim$0.2 ng/l) in order to keep the lifetime cancer risk below 10^{-5}.

*This summary has been prepared and approved by the Carcinogens Assessment Group of EPA on June 15, 1979.

Summary of Pertinent Data

The water quality criterion for PCBs is derived from the hepatocellular carcinoma and neoplastic nodule response of Sherman strain female rats fed 100 ppm Aroclor 1260 (Kimbrough, et al., 1975). A time-weighted average dose of 88.4 ppm was administered for approximately 21.5 months and the animals were observed for an additional six weeks before terminal sacrifice. The incidence of hepatocellular carcinoma and neoplastic nodules was 170/184 in the treated group and 1/173 in the control group. Assuming a fish bioaccumulation factor of 46,000, the criterion is calculated from the following parameters:

$n_t = 170$
$N_t = 184$
$n_c = 1$
$N_c = 173$
Le = 730 days
le = 645 days

d = 88.4 x 0.05 = 4.42 mg/kg/day
w = 0.4 kg
L = 730 days
R = 46,000
F = 0.0187 kg/day

Based on these parameters, the one-hit slope B_H is 3.25 $(\text{mg/kg/day})^{-1}$. The resulting water concentration of PCBs calculated to keep the individual lifetime cancer risk below 10^{-5} is 0.26 nanograms per liter.

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